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METABOLIC ACIDOSIS AND THE DISSOCIATION CURVE OF HEMOGLOBIN DURING EXTRACORPOREAL CIRCULATION

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THE PHYSIOLOGIC value of hemoglobin as an oxygen carrier lies in the fact that its affinity for oxygen is so balanced that, in the lungs, hemoglobin becomes 95 to 96 per cent oxygenated, while in the tissues and the capillaries it can give up as much of the oxygen as demanded. The relationship between oxygen tension and the degree of saturation of hemoglobin has been studied in blood and in solutions of hemoglobin by Huffner, Bohr, and others. The effect of alkalinity was first noted by Bohr, Hasselbalch, and Krogh[1] who observed that increasing carbon dioxide tension decreased the amount of oxygen bound by hemoglobin. Barcroft[2, 3] showed that the degree of oxygenation, although dependent chiefly on the oxygen pressure, also increased with the alkalinity and the electrolyte content of the blood. They subsequently showed that the effect of carbon dioxide was due to its acidity and that the addition of other acids to the blood had a similar influence. Fig. 1 depicts the S-shaped curve of oxyhemoglobin dissociation and shows the relationship between oxygen tension, oxygen saturation, and varying pH. It will be noted that, as the blood becomes more acid, hemoglobin combines with less oxygen and, as the blood becomes more

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alkaline, the opposite is noted. Conversely, the amount of oxygen which is released to the tissues is greater at a reduced pH than it is at an alkaline pH. It is this behavior which enables oxygen to dissociate from the blood as it reaches the tissues, taking up in its place carbon dioxide. The changes in oxyhemoglobin dissociation effected by changes in the pH is known as the Bohr effect.

The purpose of this study was to determine to what advantage this physiologic reaction may be applied during extracorporeal circulation. It was based on clinical observations in our own series of approximately 100 open-heart operations. In 12 instances when the arterial pH was reduced, we believed a clinical improvement and a gross color change were brought about by the addition of sodium bicarbonate to the blood during bypass.

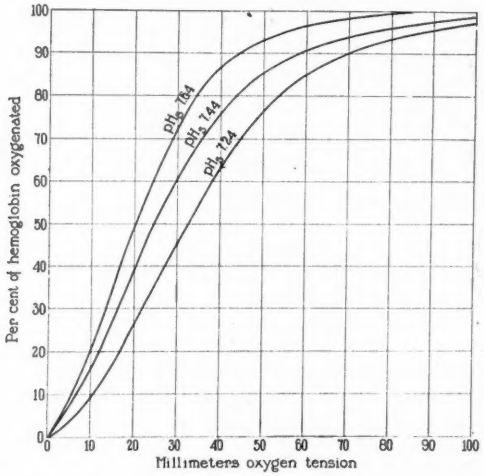

Fig. 1.—Relationship between oxygen tension and oxygen saturation of human blood at varying pH. Curves calculated by Richards and Strauss (Ref. 14).

METHOD

A. *Experimental Procedure.*—Twenty-five dogs were anesthetized with Pentothal sodium, 30 mg. per kilogram of body weight. Utilizing a multiple disk Kay-Cross oxygenator and 95 per cent oxygen and 5 per cent carbon dioxide, the animals were placed on total cardiopulmonary bypass. This was done through a right thoracotomy which was performed under aseptic technique. Venous drainage was enacted into the oxygenator by gravity after catheters were placed in the superior and inferior vena cava via the right atrial appendage. The arterial return was through the right femoral artery. The left femoral artery was cannulated with a No. 190 polyethylene catheter for continuous monitoring of the arterial pressure. This catheter was threaded into the central aorta and the pressure was determined with an aneroid manometer. A similar catheter was placed into the inferior vena cava through the saphenous vein and

connected to a saline manometer for continuous monitoring of the venous pressure. After tapes were placed around the superior and inferior vena cava, the catheters were inserted and total cardiopulmonary bypass was begun. The animals were perfused according to the amount of venous return, maintaining a venous pressure of 0 to 1 cm. of water. The animals varied in weight from 12 to 22.5 Kg. and were perfused at flow rates of 26 to 87 c.c. per kilogram a minute. After complete bypass was initiated and satisfactory flow and oxygenation were achieved, hypoxia was produced by reducing the revolutions of the disks from 120 to approximately 60 r.p.m. This caused inadequate surface area exposure, resulting in reduction of the partial pressure of oxygen and undersaturation of the blood. Particular emphasis was placed on the avoidance of changes in the blood level in the oxygenator and flow rates once the experiment was begun. With the development of hypoxia, monitoring of the pH was carried out and, as acidosis occurred due to the anoxia, the pH was noted to fall.

At a reduced pH, which averaged approximately 7.25, samples of blood at the venous inlet and the arterial outlet of the oxygenator were taken for measurement of oxygen and carbon dioxide content. The pH at the arterial end of the oxygenator was simultaneously recorded at this time. Correction of the reduced pH was then attempted by the addition of alkali or the creation of respiratory alkalosis. The alkali added was either sodium bicarbonate, 44.6 mEq. per 50 c.c. of solution or 1 M sodium-r-lactate, 1 mEq. per cubic centimeter of solution. The production of respiratory alkalosis was achieved by changing the gas mixture from 95 per cent oxygen and 5 per cent carbon dioxide to 100 per cent oxygen, thereby allowing carbon dioxide to escape from the blood.

B. *Analytical Methods.*—The following determinations were performed on the blood samples: (1) plasma pH, (2) total carbon dioxide content, and (3) total oxygen content.

Total oxygen capacity was determined from a sample taken from the oxygenator at the completion of the experiment so that complete mixing of the patient and donor blood was achieved, thereby giving an over-all hematocrit. Two of the experiments were analyzed for sodium, potassium, chloride. The pH determinations were done on whole blood at a constant temperature of 36° C. in a Beckman model G pH meter, accuracy plus or minus 0.05 pH units. Total carbon dioxide, total oxygen content, and oxygen capacity were determined according to the method of Van Slyke and Neill.[4] Sodium and potassium determinations were carried out on a Coleman flame photometer. Chloride was determined according to the method of Sendroy and his associates.[5]

C. *Calculations.*—The pCO_2* and base bicarbonate were calculated from the measured pH and the total plasma carbon dioxide, using the Henderson-Hasselbalch equation with pK′ equal to 6.10. The plasma carbon dioxide was calculated from the whole blood carbon dioxide content.[6] The per cent of oxygen saturation was calculated by dividing the total oxygen content by the total oxygen capacity and multiplying by 100. The oxygen tension of the blood was determined from the pH and arterial saturation.[7]

*Partial pressure of carbon dioxide expressed in millimeters of mercury.

RESULTS

Seven experiments were discarded because of changes in the blood in the oxygenator which could have influenced the oxygen saturation. In the remaining 18 experiments, reduction in the pH was brought about in all cases. Correction of the reduced pH was accomplished in 11 experiments by the addition of sodium bicarbonate, by the creation of respiratory alkalosis in 2, and by the addition of molar sodium-r-lactate in 1. In 4 other animals, the addition of sodium lactate failed to bring about elevation in the pH.

TABLE I. EFFECT OF CORRECTED pH*

	INITIAL				OBSERVED				CALCULATED		
EXPER. NO.	ARTERIAL pH	pO_2 (MM. Hg)	ART. SAT. (%)	VEN. SAT. (%)	ARTERIAL pH	pO_2 (MM. Hg)	ART. SAT. (%)	VEN. SAT. (%)	ARTERIAL pH	pO_2 (MM. Hg)	ART. SAT. (%)
1	7.27	48	74.0	—	7.42	48	80.8	—	7.27	48	74
2	7.18	75	88.5	55.0	7.30	80	92.8	60.8	7.18	80	90
3	7.25	70	88.6	—	7.60	62	96.0	—	7.25	62	84
4	7.27	56	81.0	56.0	7.70	32	76.5	53.0	7.27	32	50
5	7.23	43	67.2	—	7.52	35	72.8	—	7.23	35	34
6	7.35	41	70.8	—	7.59	34	75.6	—	7.35	34	42
7	7.28	58	83.5	17.4	7.35	55	84.7	16.3	7.28	55	80
9	7.26	100	99.5	—	7.45	46	82.0	—	7.26	46	70
12	7.21	55	72.0	49.3	7.26	35	60.0	17.8	7.21	35	52
15	7.14	43	58.0	23.0	7.38	30	55.0	10.7	7.14	30	48
17	7.28	66	88.0	49.3	7.54	56	92.0	49.2	7.28	56	81
18	7.24	55	79.8	35.3	7.46	46	83.6	83.6	7.24	46	69
19	7.25	103	98.0	63.5	7.61	38	81.7	43.5	7.25	38	50
20	7.28	85	94.3	61.0	7.40	56	87.9	54.6	7.28	56	80
Averages	7.25	64	81.7	45.5	7.47	47	80.1	43.3	7.25	47	65

*This table depicts the degree of oxygen saturation of the blood which was obtained when the oxygen tension was reduced and the pH simultaneously elevated by the addition of alkali or the creation of respiratory alkalosis. The calculated results are theoretical saturations which would have been expected if the pH were not corrected as the oxygen tension was decreased.

Table I depicts the pH, partial pressure of oxygen, and the arterial and venous saturation before and after the correction of the pH. In Column 3 of Table I are the calculated oxygen saturations of the arterial samples which would have been present at the reduced PO_2,* if the pH had not been corrected. It is observed (Table I) that in the 14 experiments in which the pH was corrected that the observed average oxygen saturation was 15 per cent greater than the calculated arterial saturation despite the reduction in the oxygen saturation and partial pressure.

Table II shows the arteriovenous difference which was obtained in 9 of the experiments before and after the correction of the pH. It is noted that the elevation of the pH, although allowing the blood to pick up additional oxygen during its passage through the oxygenator, did not inhibit the release of this oxygen to the tissues since the arteriovenous difference is greater, despite the shift of the oxyhemoglobin dissociation curve toward the alkaline side. This apparent discrepancy in the action of the oxyhemoglobin dissociation curve is explained below.

*Partial pressure of oxygen in millimeters of mercury.

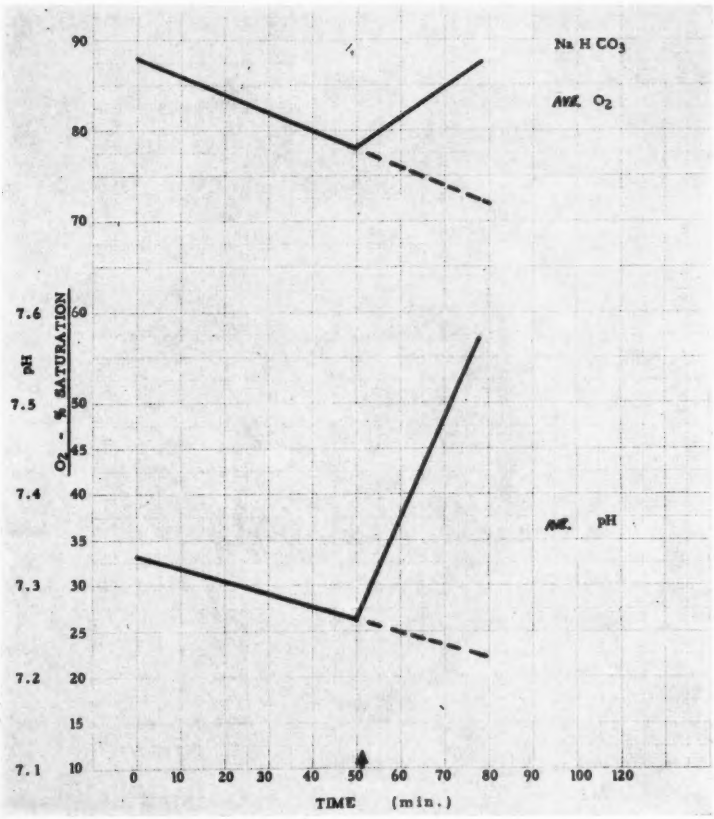

Fig. 2.—Curve showing the change in the average pH and oxygen saturation during the onset of hypoxia, and after the addition of sodium bicarbonate.

TABLE II. ARTERIOVENOUS DIFFERENCE*

EXPER. NO.	LOW pH		HIGH pH	
	ART. SAT. (%)	VEN. SAT. (%)	ART. SAT. (%)	VEN. SAT. (%)
2	88.5	55.0	92.8	60.8
4	81.0	56.0	79.5	53.0
7	83.5	17.4	84.7	16.3
12	72.0	49.3	60.0	17.8
15	58.0	23.0	55.0	10.7
17	88.8	49.3	92.0	49.2
18	79.8	35.3	83.6	46.1
19	98.0	63.5	81.7	43.5
20	94.3	61.0	87.9	54.6
Averages	82.7	45.5	80.5	39.1
A-V Difference	37.2		41.4	

*The arteriovenous difference in 9 animals before and after the correction of the pH of the blood. This shows that the correction of the pH toward the normal or alkaline range did not prevent oxygen dissociation in the capillaries.

TABLE III. SODIUM BICARBONATE*

EXPER. NO.	LOW pH	ART. O_2 (%)	ART. CO_2 (VOL. %)	pCO_2 (MM. Hg)	$BHCO_3$ (mM/L.)	HIGH pH	ART. O_2 (%)	ART. CO_2 (VOL. %)	pCO_2 (MM. Hg)	$BHCO_3$ (mM/L.)	$NaHCO_3$ (mEq.)	TIME (DIF. MIN.)
1	7.27	74.0	—	—	—	7.42	80.8	—	—	—	133.8	63
2	7.00	85.5	40.5 (% Sat.)	—	—	7.30	95.8	85.1 (% Sat.)	—	—	624.4	55
3	7.25	88.6	29.9	33.8	14.4	7.60	96.0	65.5	37.0	35.0	156.1	20
4	7.25	70.4	—	—	—	7.70	79.5	—	—	—	156.1	75
5	7.23	67.2	—	—	—	7.52	72.8	—	—	—	89.2	25
6	7.20	68.8	—	—	—	7.59	75.6	—	—	—	111.5	25
7	7.28	83.5	8.4	7.2	4.25	7.78	86.3	34.0	13.5	19.4	89.2	30
9	7.17	95.1	38.9	51.7	17.9	7.45	82.2	75.1	58.5	39.3	133.8	35
15	7.14	88.7	43.8	66.0	22.0	7.38	55.5	40.2	36.7	20.8	44.6	9
19	7.25	97.4	36.0	50.8	17.2	7.61	98.2	54.7	46.5	27.6	44.6	19
20	7.13	90.8	28.9	43.3	14.1	7.40	87.9	45.3	40.3	24.1	44.6	17

*The results in eleven of the experiments in which sodium bicarbonate was used to correct the acidosis. The last two columns show the number of milliequivalents given and the time in minutes between the lowest and highest pH determinations.

Table III and Fig. 2 illustrate the changes in those animals which received sodium bicarbonate. The pCO_2 and $BHCO_3$ determined in 6 of these experiments shows that the addition in the total carbon dioxide content of the blood is reflected as an increase in the $BHCO_3$.

TABLE IV. SODIUM LACTATE*

EXPER. NO.	LOW pH	ART. O_2 (%)	HIGH pH	ART. O_2 (%)	TOTAL LACTATE (C.C.)	TIME (DIF. MIN.)	O_2 & CO_2 (%)
11	7.48	94.02	7.24	96.66	120	34	95 & 5
12	7.21	72.95	7.36	60.26	80	35	95 & 5
13	7.32	94.11	7.29	72.21	200	38	95 & 5
14	7.29	77.13	7.21	63.10	160	50	95 & 5
16	7.28	93.70	7.14	88.68	160	25	95 & 5

*The results in 5 animals given 1 M sodium-r-lactate solution. Note the failure to change the pH of the blood, and the continued fall in oxygen saturation. The time differential is the time between the addition of lactate and the taking of the sample for pH and oxygen saturation. Column 3 is labeled "high pH" and is the pH after the addition of sodium lactate. Note the failure to raise the pH in four of the five experiments.

Table IV depicts the results in those animals who received sodium lactate 150 to 200 c.c. of a molar solution. Four of the 5 animals failed to show any change in the pH of the blood. In 2 experiments, a change in the pH was induced by the development of respiratory alkalosis. This is illustrated in Table V and shows that respiratory alkalosis can induce a marked change in the pH. No striking change in the arteriovenous difference was noted so that the amount of oxygen delivered to the tissues was apparently not increased.

TABLE V. RESPIRATORY ALKALOSIS*

	pH	ART. O_2 SAT. (VOL. %)	ART. CO_2 (VOL. %)	ART. pCO_2 (MM. Hg)	ART. $BHCO_3$ (mM/L.)	VEN. O_2 (VOL. %)
Experiment 17						
95% O_2 and	7.21	15.69	52.01	52.3	21.7	8.95
5% CO_2	7.28	15.20	55.94	51.0	23.5	—
100% O_2	7.40	15.24	46.45	33.0	19.8	8.22
	7.54	15.44	45.54	23.8	19.8	8.21
			Capacity 16.88			
Experiment 18						
95% O_2 and						
5% CO_2	7.24	14.23	51.89	52.0	22.5	6.29
100% O_2	7.46	14.90	40.24	25.1	17.3	8.21
			Capacity 17.84			

*The effects of respiratory alkalosis produced in 2 animals by removing carbon dioxide from the oxygenating mixture. Note the marked reduction in pCO_2.

DISCUSSION

The design of the experiment was to reproduce the clinical situation resulting in inadequate oxygenation of the patient during cardiopulmonary bypass. This has been shown to result in a gradual production of metabolic acidosis.[8] Clinically this can occur if the flow rate of the patient exceeds the oxygenating capacity of the oxygenator or by the opposite situation of inadequate venous return because of insufficient gravity, faulty placement of the caval cannulae,

or blood loss. This will result in inadequate arterial output and, despite adequate oxygenation of the blood as it passes through the oxygenator, the total amount of oxygen delivered to the patient will not supply his demand. The situation to a lesser degree may also be encountered if the donor blood is improperly stored and glycolysis markedly reduces the pH of the blood. This latter situation may be particularly compounded in those patients with cyanotic heart disease in whom it has been shown that some degree of metabolic acidosis is present.[9] These patients frequently, during preparation for bypass, will have a reduced cardiac output with hypotension and additional acidosis may occur before actual bypass is begun. Considerable desaturation of the tissues may be present and, if a high flow rate cannot be achieved to correct this during bypass, further acidosis and desaturation of the blood occurs, resulting in a markedly desaturated venous return which may overtax the efficiency of the oxygenator. The net result in these situations is a fall of oxygen tension, inadequate oxygen saturation, tissue hypoxia, and metabolic acidosis.

The body has two main lines of defense to prevent further hypoxia. They are the favorable dissociation of oxyhemoglobin at low oxygen tissue pressures and the reinforcement of this effect by the pH gradient between the arterial and capillary blood favoring further release. Because of the S-shaped curve of oxyhemoglobin dissociation it was necessary to illustrate these effects in our experiments to reduce the oxygen tension of the blood to approximately 30 to 50 mm. Hg. As is illustrated in Fig. 1, at higher oxygen saturations, changes in pH would not well illustrate the Bohr effect. As the disk speed was reduced, however, it was impossible to achieve a constant oxygen tension since the animal was continuously depleting the oxygen content of the arterial return and, during the time that the bicarbonate, lactate, or respiratory alkalosis was effected, further reduction in the tension took place. We, therefore, determined the oxygen tension at the pH and oxygen saturation of the arterial blood before and after the correction of the pH and calculated what the saturation of the arterial blood would have been at this reduced oxygen tension if the pH had not been corrected. This is shown in Table I. In those instances in which the arterial saturation was within normal range and in which oxygen tension was only mildly reduced when the pH was concomitantly reduced the addition of sodium bicarbonate actually raised the oxygen saturation, illustrating the true Bohr effect, that is, an increase in the oxygenation of the blood by the addition of alkali at a constant oxygen tension. In the remaining instances, although the correction of the pH did not raise the oxygen saturation of the blood, when compared to the initial sample, this could not be expected because of the continuing drop in oxygen tension. It did, however, prevent a further loss of saturation since, despite the further reduction in oxygen tension, an almost similar average arterial oxygen saturation was achieved. The fundamental question to be answered, however, was the method by which the arterialized blood achieved greater saturation. Was this at the expense of the tissues? Did the elevation of the pH in effect prevent release to the tissues so that the arteriovenous differences before and after the correction of the pH were essentially similar?

Table II shows the arteriovenous differences and, on the average, the tissues were able to extract more oxygen after the correction of the pH than before. It will be noted that at the higher oxygen saturations the change in arteriovenous difference was insignificant despite the correction of the pH. However, at the reduced saturations there were greater arteriovenous differences. This can be explained from the dissociation curve. At the higher saturations, pH has little effect on dissociation, but at reduced tensions it becomes quite significant. For example, Fig. 3 is a line chart showing the amount of oxygen bound by the hemoglobin of the blood of Dr. A. V. Bock at varying oxygen tensions and serum pH. At 30 mm. of oxygen tension, increasing the pH from 7.25 to 7.70

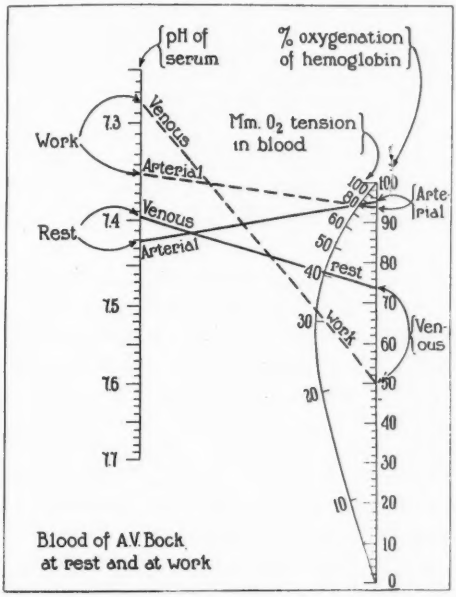

Fig. 3.—Line chart showing the amounts of oxygen bound by hemoglobin of the blood of Dr. A. V. Bock at different serum pH and oxygen tension (Ref. 7).

increases oxygenation 35 per cent. The converse of this is also illustrated in Fig. 3 where the slight lowering of the blood pH when it receives carbon dioxide from the tissues assists in releasing additional oxygen. Thus, from the above chart, it is evident that if Dr. Bock at work had maintained an arterial pH in the capillaries, a drop to 32 mm. of oxygen tension in the capillaries would have left 56 per cent of the venous hemoglobin in the oxygenated state instead of the observed 50 per cent. This represents 13 per cent of the total oxygen released from the blood that is due to the slight lowering of the pH.

The effect of oxygen tension in vivo is illustrated in Fig. 1. At pH 7.4, the first 30 mm. of oxygen tension grosses 56 per cent oxygenation of the hemoglobin in contrast to an increase of 30 mm. of tension at the top of the scale changing

the oxygenation only 6 per cent. When unusual demands in the tissue require oxygen, the last 30 mm. of oxygen tension causes a yield of more than half the arterial oxygen content. It is evident that at high oxygen tensions the addition of alkali to the blood will have little physiologic advantage but in situations as may occur during extracorporeal circulation in which the arterial saturation is reduced and tissue hypoxia is present, the correction of the pH toward the alkaline side will allow greater uptake of oxygen in the oxygenator, but will not affect the tissue pH to the extent that it will not be able to extract this additional oxygen from the blood as it reaches the tissue. We believe from our results that the correction of the pH allowed the blood to combine with more oxygen during its passage through the oxygenator increasing the total amount of oxygen available. However, on reaching the tissues the reduced oxygen tension and the additional tissue acidosis more than offset the increased oxygen affinity brought about by the change to the alkaline side, and therefore more oxygen was actually released to the tissues. In addition, by preventing further desaturation of the venous return additional strain on the oxygenator was prevented. The cycle of events which could be brought about by further venous desaturation, that is, reduced arterial saturation, reduced tissue oxygen tension, further extraction of oxygen, and a further reduction in venous saturation, was ameliorated.

One of the practices which is carried out during cardiac surgery is to hyperventilate the patient prior to bypass, creating a respiratory alkalosis and an elevated pH. This change in pH should favorably effect the oxyhemoglobin dissociation curve if severe hypoxia is present as illustrated above. However, recent work[10, 11, 12] has shown that hyperventilation is accompanied by increased production of lactic acid. This is predominantly an intracellular acidosis and is accompanied by an exchange of sodium for hydrogen ion. Elkinton and his co-workers[11] have shown that in acute respiratory acid-base disturbances transfer of intracellular cation occurs probably as the result of the changes of extracellular pH. No positive or negative load of fixed cation is imposed on the body as in the case of metabolic disturbances. Ninety per cent or more of the change in effective extracellular bicarbonate was extrarenal[10] and was related to changes in hydrogen ion uptake or release by buffer protein in the blood and by ionic transfer into or out of the cellular fluid in the body. Their results in respiratory alkalosis indicate that part of the cellular buffering consisted in release of hydrogen ion with the release of an undetermined ion, probably lactate, since an increase of extracellular lactic acid has been specifically reported to occur with respiratory alkalosis.[12, 13] Thus, it would appear that deliberate introduction of respiratory alkalosis before bypass would result in increased lactic acid formation and be actually more detrimental to the patient during extracorporeal circulation.

Table II illustrates the failure of sodium lactate to produce any change in the pH of the blood in 4 of the 5 animals when it was added during extracorporeal circulation. The lactate was administered rapidly and the animal received approximately 150 to 200 c.c. of molar sodium lactate in a half-hour period. Although the blood sodium following lactate administration became

elevated, obviously sufficient time had not elapsed for the metabolism by the liver to release bicarbonate. During extracorporeal circulation to effect changes in pH, sodium lactate is apparently not rapidly enough metabolized to effect these changes.

With the present improvements in pump-oxygenators and the greater experience gained from their application, oxygenation of blood does not now appear to be a significant problem. However, occasionally situations do arise in which, because of blood loss or lack of blood reserve in the system, a compromise on the flow rate may become necessary. Under these circumstances, increasing metabolic acidosis will result and the addition of sodium bicarbonate to counteract the release of lactic acid in this situation appears to be indicated. During the past year we have continuously monitored pH of the blood during bypass and if the pH falls below 7.3 sodium bicarbonate, 4 mEq. per kilogram of body weight is given directly into the oxygenator. This has been given over a 10-minute period on 12 different patients and it has been noted in these cases to effect correction of the pH and at times a gross improvement in the oxygenation of the blood. In these cases, we have not observed any adverse effects and found that postoperative acidosis, as illustrated by urine pH and blood pH determinations which would have been expected in these cases, has not been a problem.

SUMMARY

Eighteen mongrel dogs were placed on extracorporeal bypass and metabolic acidosis was deliberately introduced by underoxygenation of the blood. When the pH of the blood was lowered, blood samples were taken for arterial and venous oxygen saturations. The pH was then corrected in 14 of these animals. It was done by the addition of sodium bicarbonate in 11 with the creation of respiratory alkalosis in 2 and the addition of sodium lactate in 1; the addition of sodium lactate in 4 other animals failed to affect any change in the pH. Oxygen tension was determined from the pH and the saturation of the blood at the corrected pH and compared to the calculated oxygen saturation of the blood at the same oxygen tension if the pH were not corrected. The data illustrated that the Bohr effect, particularly at reduced oxygen tensions, raised the oxygen saturation of the blood during its passage through the oxygenator approximately 15 per cent. Despite the correction of the pH, a greater arterial venous difference was noted, thereby effecting greater transport of oxygen to the tissues. The effect of sodium lactate was found in 4 out of 5 animals to be ineffective in creating a pH change. This is explained by the inadequate time elapsed between the addition of lactate and the pH determinations to allow for sufficient metabolism of the lactate. Respiratory alkalosis was effective in 2 animals in elevating the pH and the physiologic effects of respiratory alkalosis were briefly discussed. The clinical application of the results of this experiment was briefly presented.

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(For Discussion, see page 638.)

STUDIES OF EDGLUGATE-Mg: A NEW DONOR BLOOD ANTICOAGULANT—PRESERVATIVE MIXTURE FOR EXTRACORPOREAL CIRCULATION

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THE clinical application of extracorporeal circulation brought with it the need for relatively large amounts of heparinized blood freshly drawn from compatible donors. Already, the increasing use of this essential but sanguivorous adjunct to modern cardiovascular surgery is placing such a burden on some blood banks and donor programs as to interfere seriously with their efficient operation and their provision of blood for ordinary needs. In some localities, this "fresh blood" problem has been the major factor limiting both the frequency and convenient scheduling of open heart operations. When, after the donor blood is drawn, such operations are canceled, or the intended extracorporeal circulation not employed, blood banks have on short notice the unhappy choice of quickly finding other suitable recipients for this group specific blood of short storage life or of discarding it altogether as waste. In such cases, the expedient of re-entering the blood container to add a second anticoagulant—preservative solution such as acid-citrate-dextrose (ACD) is unacceptable because of the potential hazard of bacterial contamination.

The design of an ideal donor blood anticoagulant—preservative mixture for use in extracorporeal circulation should consider the desires of the following:

Blood banks would like (1) to accumulate donor bloods 1 to 5 days preoperatively; (2) to use conventional, inexpensive donor equipment; and (3) if the blood is not used for extracorporeal circulation (a) to avoid re-entry of container with anticoagulant—preservative mixture and (b) to use for routine transfusions up to 2 to 3 weeks of storage.

The surgeon would like (1) relatively fresh blood with (a) good osmotic and mechanical resistance, (b) maximal red blood cell viability, (c) intact coagulation components; (2) anticoagulant—preservative mixture permitting (a) minimal dilution of blood, (b) compatible plasma electrolyte pattern, (c) no clots or fibrin, (d) near normal pH (at 37° C.); (3) to have blood on hand at all times for emergency perfusions.

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The patient's family would like to avoid the cost of professional donors.

Blood donors would like to donate blood at their convenience during the 5 days before operation.

In the hope of fulfilling most of these desires, we began studies of various anticoagulant—preservative mixtures about 2 years ago. These studies included certain exchange resins and sequestering agents combined with sugars and stabilizing salt solutions. Of the numerous combinations studied thus far, only a mixture of disodium ethylenediamine tetraacetic acid, glucose, sodium gluconate, and magnesium chloride has shown sufficient promise to warrant clinical trial. This report describes a portion of our most significant studies of this anticoagulant—preservative mixture and records our clinical experience employing it for donor blood during the past few months.

MATERIALS AND METHODS

The composition of Edglugate-Mg,* the solution finally adopted and upon which these studies are based, is given below.

$Na_2H_2EDTA{\cdot}2H_2O$	0.41 Gm.
Sodium gluconate (anhyd.)	0.364 Gm.
Dextrose (anhyd.) USP	1.50 Gm.
$MgCl_2{\cdot}6H_2O$	0.305 Gm.
Water q.s. ad	30.0 ml.

The above mixture in a volume of 30 c.c. was prepared and sterilized in plastic bag containers.

After venipuncture, 500 c.c. (530 Gm.) of whole blood were drawn into each bag by gravity with frequent agitation to ensure complete mixing. Care was taken not to overfill any of the bags. The bags of blood were then stored in a blood bank refrigerator at 2° to 6° C. until shortly before use.

Conversion for Priming Blood in Extracorporeal Circulation.—Only bags of blood which had been stored *for 5 days or less* were used in priming the heart-lung machine and filling the extracorporeal reservoir. For this use, each bag was first "converted" (Fig. 1) by adding 15 mg. (1,500 units) of commercial heparin by syringe and needle through the rubber bung of the bag closure. After thorough mixing, 5 c.c. of a sterile aqueous solution of calcium chloride containing 1.67 mM of Ca^{++} (0.2425 Gm. calcium chloride USP) was added to each bag in order to restore the ionized calcium to slightly above the normal blood level. After mixing thoroughly by tilting the bag, the blood was introduced into the extracorporeal apparatus or reservoir. In most instances the "conversion" of these donor blood units was carried out within 15 to 30 minutes of the start of the perfusion.

Bags of blood not used for extrocorporeal circulation, but employed for routine transfusions, were stored for various intervals up to 21 days before administration. For this purpose no "conversion" or additives were employed, the blood being administered as any ordinary transfusions directly after removal from the blood bank. In many instances, samples of blood were taken

*This solution was prepared and supplied to us in sterile plastic containers by the Cutter Laboratories, Berkeley, Calif.

aseptically from each bag just before use for the various determinations listed below. A large number of bags of blood were drawn from donors and stored for study purposes only. Sterile samples were drawn from these bags for various studies at regular intervals throughout the refrigerated storage period. Because of the multiple re-entries into these bags with the potential danger of contamination, they were not considered suitable for transfusion purposes.

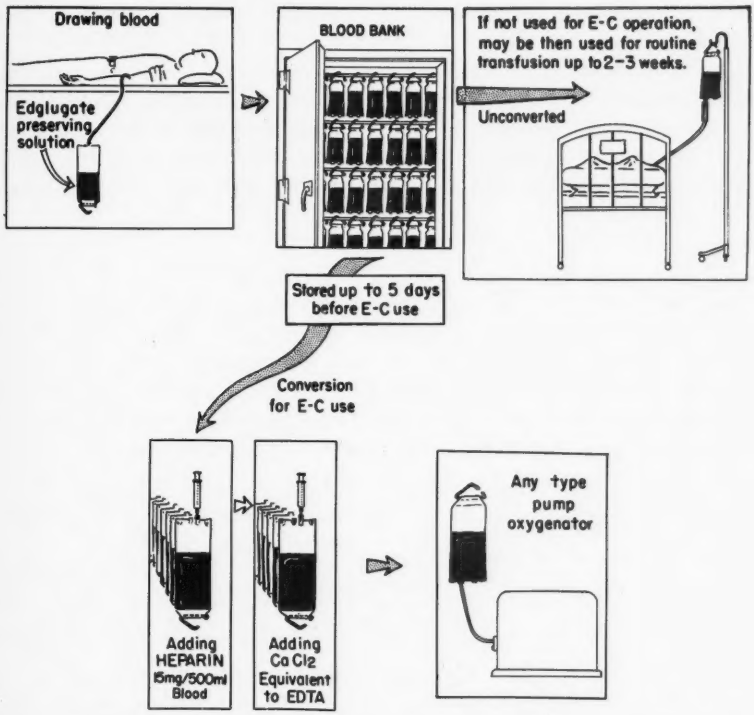
Drawing blood
Edglugate preserving solution
BLOOD BANK
If not used for E-C operation, may be then used for routine transfusion up to 2–3 weeks.
Unconverted
Stored up to 5 days before E-C use
Conversion for E-C use
Adding HEPARIN 15mg/500ml Blood
Adding Ca Cl2 Equivalent to EDTA
Any type pump oxygenator

Fig. 1.—Picture diagram of collection, storage, and alternative uses of Edglugate blood. The amount of blood being collected is measured by a carefully calibrated spring scale. During drawing the plastic bag and its contents are frequently agitated and kneaded to ensure swift thorough mixing of blood with anticoagulant. For conversion we have found that 15 mg. (1,500 units) of heparin and 1.65 mM $CaCl_2$ per 500 c.c. unit of blood are satisfactory. This amount of $CaCl_2$ is 50 per cent excess over theoretical to offset the physiologic effect of the elevated plasma K^+ level of the blood. Filtering the blood while priming the pump-oxygenator may be advisable depending upon the design of the equipment and the adequacy of the blood drawing technique.

Clinical perfusion equipment and techniques used in our hospital have been described previously.[1] Hypothermia produced by a blood heat exchanger[2] was employed in all cases and each patient was on partial perfusion for 3 to 10 minutes during the cooling phase before total bypass was begun. Flow rates averaged 50 c.c. per kilo per minute for patients weighing 35 Kg. or less and 30 c.c. per kilo per minute for patients weighing over 35 Kg. Duration of perfusions ranged from 15 minutes to 1 hour and 20 minutes.

Laboratory determinations of whole blood pH, blood oxygen content,[3] blood CO_2 content, blood buffer base,[4] sodium and potassium, plasma hemoglobin, erythrocyte osmotic fragilities, partial thromboplastin times,[5] blood clotting times, recalcification clotting times, fibrinolysin activity, plasma fibrinogen,[6] and plasma factor V assay[6] were made by the methods referred to or by other standard procedures. Antihemophilic globulin (AHG) assays were carried out by the partial thromboplastin time method of Langdell,[7] employing plasma from a known severe hemophilic patient with an AHG level of less than 1 per cent.

Determinations of in vivo red cell survival after various intervals of blood storage at 2° to 6° C. were made by autotransfusions in healthy volunteer subjects. The red cells in these survival experiments were tagged with Cr^{51} by the method of Read.[8] The initial red cell volumes of these recipients were determined by tagging separate aliquots of their own fresh red cells with P^{32}.

RESULTS

In Vitro Studies.—The results of in vitro studies of Edglugate blood after various intervals of storage at 2° to 6° C. are given in Table I. The most significant changes noted were an increase in plasma potassium levels, a prolongation of the partial thromboplastin time, and a decrease in the level of accelerator globulin (Factor V). The plasma potassium level was seen to rise to a plateau of around 25 mEq./L. after about 5 days of storage.

TABLE I. CHANGES OCCURRING IN EDGLUGATE-Mg BLOOD DURING STORAGE AT 2° TO 6° C.

DAYS STORAGE AT 2°-6° C.	pH 37° (MEDIAN)	K (mEq./L.)	Na (mEq./L.)	PTT (SEC.)	AHG LEVEL (%)	FACTOR V (%)	RECAL. CLOT. TIME (MIN./SEC.)	PLATELETS (THOUS./MM.^{3})	FIBRINOGEN (MG./100 ML.)	PLASMA Hb (MG./100 ML.)
0	7.17	6.2	141	(73)	89	(100)	3/30	258		2*
1	7.12	10.1	141				3/46	173		
2	7.08	15.0	141	181	49	18	3/51	213		
3	7.06	18.5	141	168			3/46	206		6†
4	7.03	19.9	141	129	20	6.1	4/21	226		
5	6.99	24.5	142	130	15	9.7	4/03		340	2*
6-10	7.0	27	131	144		9.7			301	12†
11-15	7.1	29	127	240		9.7			308	3*
16-20	7.2	27	132	357		0.7			292	

Each value in this table represents the average (or median) value obtained from studies of at least 10 pints of Edglugate donor blood. Some values represent studies on more than 600 pint units.

Average values in parentheses were obtained from citrated blood samples drawn from donors just prior to their 500 c.c. donations into the Edglugate-Mg bags.

*Average values of bags not agitated prior to sampling.

†Average values of same bags thoroughly mixed before each sampling.

Antihemophilic globulin levels were assayed on a group of Edglugate donor bloods after 2, 4, and 5 days of storage. There was a slight fall immediately after drawing the blood with a progressive decline to about 15 per cent of normal by the fifth day of storage.

The level of Factor V (accelerator globulin) also declined with storage, falling to about 10 per cent at the end of 5 days. There was some gradual

increase in the recalcification clotting times during the first 5 days. Platelet counts remained remarkably stable during this time, but with some variation in counts on individual bags. Fibrinogen levels even at 20 days showed only an insignificant change. Plasma hemoglobin levels did not show any significant increase during the storage period unless the bags were repeatedly mixed and allowed to resettle. Under these circumstances there was a slight increase in plasma hemoglobin level that averaged less than 12 mg. per cent after 6 to 10 days of storage. Whole blood pH determinations made at 37° C. remained relatively constant during the entire 20-day storage period in the range of 7.0 to 7.2.

The results of in vivo red cell survival studies of Edglugate blood compared with blood stored in standard acid citrate dextrose after varying storage periods up to 21 days are represented by the curves in Fig. 2.

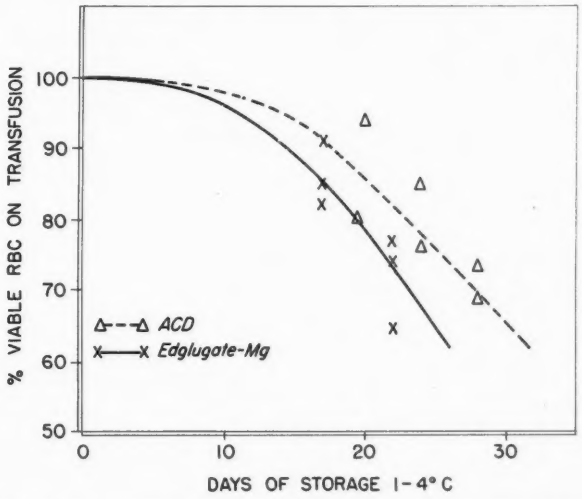

Fig. 2.—The in vivo viability of autotransfused erythrocytes of blood stored in Edglugate solution (*solid curve*). A curve of ACD blood erythrocyte survival (*broken line*) is included for comparison. Edglugate blood has an erythrocyte viability of 73 per cent after 21 to 22 days of storage.

It will be noted that there was no significant difference in red cell viability between bloods in these two anticoagulants during the first week of storage, both solutions providing better than 95 per cent survival. At the end of 21 days' storage, Edglugate bloods showed survivals averaging approximately 72 per cent viable red cells whereas ACD bloods of the same age showed a slightly better viability with 78 per cent of the transfused cells surviving normally.

Clinical Studies.—Table II summarizes certain data on the 81 patients undergoing clinical perfusions in which Eglugate-Mg donor blood from 1 to 5 days old was used exclusively for priming the heart-lung machine and reservoir. Here the volumes of Edglugate blood employed have been expressed in

TABLE II. EXTRACORPOREAL CIRCULATION PATIENTS PRIMING VOLUME EDGLUGATE-Mg BLOOD PER KILOGRAM BODY WEIGHT

VOLUME EDGLUGATE BLOOD	75 C.C./KG.	75-150 C.C./KG.	150-225 C.C./KG.	225-300 C.C./KG.	300 C.C./KG.
Body wt. range Kg.	45-97	22-59	15-27	12-16	3-12
No. patients	37	19	12	6	7
No. deaths	8	3	1	2	5
Platelet counts % of control*	35	43	48	34	34
Serum K % of control†	91	101	103	112	125

*Average platelet counts approximately 15 minutes postperfusion expressed as per cent of patient's pre-perfusion platelet count.

†Average serum potassium levels immediately postperfusion expressed as per cent of patient's pre-perfusion serum potassium level.

terms of the patients' weights in order to make better comparison of the donor blood priming volumes with the patients' original blood volumes. The number of patients in each volume-weight range is shown with the number of deaths in each group. Most of the deaths, 14 out of 19, occurred at the extreme ranges of donor priming volume to patients' weights. The number of patients and deaths are tabulated according to diagnosis in Table III. Most of the

TABLE III. OPERATIONS WITH EXTRACORPOREAL CIRCULATION EMPLOYING EDGLUGATE PRIMING BLOOD 1 TO 5 DAYS OLD

DIAGNOSIS	NO. PATIENTS	POST-OPERATIVE BLEEDING	DEATHS
Open-Heart Cases			
Atrial septal defects	18	0	0
Ventricular septal defects	10	1	3
Tetralogy of Fallot	13	0	2
Mitral stenosis or insufficiency	15	0	4
Pulmonic or aortic stenosis	13	0	2
Tricuspid atresia	1	0	1
Complete transposition	2	0	2
Total anomalous pulmonary venous drainage	2	0	1
Totals	74	1	15
Miscellaneous Perfusions			
Thoracic and ventricular aneurysms	4	0	3
Cerebral aneurysms and tumors	3	0	1
Totals	7	0	4

deaths in this series occurred among the patients with the most complicated and serious lesions. The average decrease in platelet counts postperfusion ranged between 52 and 66 per cent of the pre-perfusion counts for all the groups of patients.

There was only a slight rise in the average postperfusion serum potassium levels, reaching 25 per cent or approximately 1 mEq./L. more than the pre-perfusion level in only the smallest patients in whom the volume of priming blood exceeded the patient's blood volume fourfold or more. When the priming donor blood had the highest plasma K levels and particularly when the patients were small with a high ratio of donor priming blood to patient's weight, a rise in the patient's serum K^+ level was occasionally seen a minute

or so after starting the perfusion (Fig. 3). This rise in K rarely persisted more than 2 to 4 minutes and quickly fell and remained at normal levels during the remainder of the perfusion.

Changes in various blood coagulation components in 5 patients following perfusion with Edglugate blood are shown in Table IV.

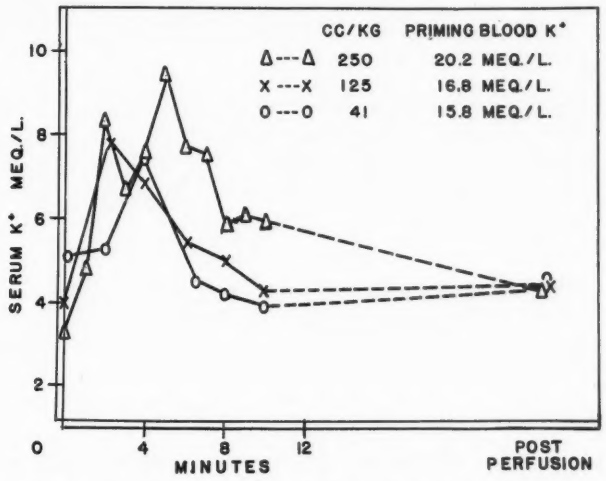

Fig. 3.—Graph showing the change with time of the plasma K^+ levels in the venous return blood of 3 patients immediately after the start of extracorporeal perfusion with stored Edglugate blood. Volumes of pump priming blood per kilogram of patient body weight and the plasma K^+ level of the blood at the start of perfusion are tabulated in the upper right (see text).

TABLE IV. COAGULATION CHANGES IN PATIENTS PERFUSED WITH EDGLUGATE-Mg BLOOD

PT.	WT. KG.	E-G-G BLOOD (C.C.)	AVG. AGE (DAYS)	DURATION ECC (MIN.)	PLATELETS (THOUS./MM.^{3})	COAG. TIME (MIN.)	AHG (%)	FACTOR V	LYSIN
A	32	4,000	2	39					
Pre-perfusion					435	7	100	100	0
Postperfusion					173	7	100	55	0
B	21.3	4,000	2	69					
Pre-perfusion					223	5	100	100	0
Postperfusion					193	9	48	49	0
C	12.3	3,500	3	54					
Pre-perfusion					303	6	100	100	0
Postperfusion					223	14	42	17	0
D	12.3	4,000	3	46					
Pre-perfusion					428	5	100	100	0
Postperfusion					153	12	1	30	+++
E	14.8	4,000	2	59					
Pre-perfusion					395	6	100	100	0
Postperfusion					75	4	14	35	0

The distribution as to single, multiple spaced, and large simultaneous transfusions totaling 945 units of blood administered throughout the hospital as ordinary transfusions without "conversion" is listed in Table V.

TABLE V. DISTRIBUTION OF EDGLUGATE-Mg BLOOD AS ORDINARY TRANSFUSIONS GIVEN AS SINGLE AND SPACED OR LARGE TRANSFUSIONS (WITHIN 24-HOUR PERIOD) AFTER STORAGE AT 2°-6° C. UP TO 21 DAYS

	PINTS TRANSFUSED				
	1	2-4	5-8	9-12	12+
Patients receiving single or spaced transfusions	274	107	18	4	3
Patients receiving large transfusions	—	115	12	3	1
Total pints transfused—945					

DISCUSSION

While heparin is the only in vivo anticoagulant which has been found suitable for extracorporeal perfusion use, it is a poor anticoagulant for preserving donor blood for any length of time. Blood collected in heparin slowly escapes the anticoagulant effect and within 12 to 30 hours of storage usually becomes unfit for perfusion use.

Proper storage of donor blood for more than a few days requires more than the simple prevention of coagulation. Various substances must be added and physical conditions adjusted to minimize deterioration of both cellular and protein elements during storage. For example, without added glucose, erythrocytes soon lose viability which may not be signaled by hemolysis or changes in osmotic or mechanical fragility. When such red cells are returned to the circulation they are rapidly destroyed.

Certain coagulation components, particularly Factor V and AHG, disappear fairly rapidly from stored blood, and especially so if incipient clotting is started by faulty collection. No satisfactory way has yet been devised to extend the naturally short life spans of leukocytes and platelets in vivo or in vitro. These formed elements may appear morphologically normal in stored blood and yet be nonfunctional and nonviable after transfusion. Thus good platelet counts are probably meaningless on blood stored beyond 36 to 48 hours.[9]

Successful storage of whole blood for perfusion purposes depends upon devising a solution which preserves as far as possible the coagulation components, the erythrocytes and, within the limits of their natural life span, the blood platelets. The anticoagulant isotonicity, pH, dilution, and the presence or absence of various substances all affect the storage characteristics of different components of blood drawn into the mixtures.

Edglugate-Mg solution was devised as an anticoagulant—preservative mixture for donor blood which might be suitable for extracorporeal perfusion use up to 5 days' storage and ordinary transfusion use up to 21 days' storage. Sprague and his associates[10] showed that a mixture of EDTA (ethylenediamine tetraacetic acid) and glucose was a suitable anticoagulant preservative solution, at least with respect to red cell viability. EDTA has been used clinically as an anticoagulant for blood transfusions for some time, particularly for transfusions where platelet rich blood is desirable.

The disodium calcium salt of EDTA (the compound resulting on its addition to blood) has a very low toxicity in man. Administered as a chelating

agent for toxic polyvalent cations, it has been used extensively for lead poisoning in children and for accidental ingestion of various radioisotopes. The only significant toxic effect reported thus far has been renal tubular damage after its prolonged use for lead intoxication.[11] None of this compound is metabolized and it is rapidly excreted by the kidney.

Disodium EDTA is a powerful sequestering agent of divalent cations and on a molar basis is five times as efficient as sodium citrate as an anticoagulant of blood.

Initial studies were made to find the least amount of EDTA which could be relied on to prevent even traces of coagulation in donor blood drawn by routine blood bank procedure. These studies revealed that the EDTA-Ca^{++} binding is not complete at normal blood pH and that a slight excess of EDTA is required above the stoichiometric quantity of calcium. We have found 1.1 mM of disodium EDTA to be a satisfactory amount for anticoagulating 500 c.c. of blood.

There is a sharp chemical equivalence relationship between Ca^{++} and the EDTA which permits the ionized calcium in blood anticoagulated with a minimum of EDTA to be restored rather precisely with a predictable minimum amount of a calcium salt. Actually, 1.1 mM of Ca^{++} results in a restoration of the blood ionized calcium level to a normal value in the presence of the inert calcium disodium EDTA complex. However, in the conversion of Edglugate blood for perfusion purposes we have chosen to add 1.65 mM Ca^{++} in view of the increased potassium content of the plasma which develops during the permissible storage period.

In our conversion of Edglugate blood for perfusion, we have added 15 mg. (1,500 units) of heparin just prior to the addition of the calcium chloride solution.

This principle of "conversion" of Edglugate-Mg blood with heparin and calcium ion raises the question of the feasibility of "converting" standard ACD blood for extracorporeal perfusion. Even though we are aware that this has been done by some heart surgical teams in desperate situations of large unexpected blood loss, ordinary ACD blood has certain characteristics which seriously detract from using it as the only source of priming blood. This blood is more dilute and carries with it a considerable burden of added sodium ion. In addition, it has a pH at body temperature which may be unacceptably low for extracorporeal perfusion during heart-lung bypass. Considerable citrate in excess of blood calcium must be present in ACD solution to force sufficient sequestration of Ca^{++} to prevent the blood from clotting. Even if the dilution and sodium burden were to be considered acceptable, the successful "conversion" would require the addition of a large and uncertain amount of calcium ion to the blood to equilibrate with the excess citrate, and some acceptable organic or mineral base should be added to adjust the pH.

In order that Edglugate blood might be preserved in storage for ordinary transfusions, should it not be used for extracorporeal circulation, glucose was added to the mixture. It has been shown previously[10] that the combination of

EDTA and glucose gives satisfactory survival of red blood cells after storage up to 21 days. However, whereas we also found this combination to give good in vivo survival (see Fig. 2), we noted an increase in hemolysis and plasma hemoglobin between the second and third weeks of storage. We found this mild spontaneous hemolysis could be largely prevented by the addition of a small amount (1.67 mM) of sodium gluconate to the anticoagulant mixture.

The leakage of potassium ion from red cells to the plasma during the refrigerated storage of whole blood seems to be an unavoidable phenomenon which is influenced by the nature of the anticoagulant—preservative employed only in rate. Red blood cells stored in Edglugate lose potassium at a rate about double that of ACD blood. From the standpoint of its use in perfusions, this is perhaps the most important defect of this mixture.

We are hopeful that further adjustments of this anticoagulant—preservative still under study may decrease this rate of potassium loss with storage. Perhaps chelating the additional plasma potassium and any ammonia accumulated during storage on exchange resins at the time of transferring the blood into the heart-lung machine might be a practical solution, but thus far we have had no experience with this interesting technique recently suggested by Schechter.[12]

As illustrated in Fig. 3, a transient rise of plasma potassium occurs in some patients perfused with Edglugate blood within 2 to 3 minutes after starting perfusion. There is a simple correlation between the level reached and the potassium content (related to the age of the blood), volume of priming blood, and body weight of the patient. This additional plasma potassium is quickly taken up by the patient's relatively large intracellular space and the plasma potassium returns to normal in the next 2 to 4 minutes of perfusion.

As would be expected, the pH of Edglugate blood declines slightly during storage as the erythrocytes metabolize glucose and liberate free organic acids to the plasma. However, this fixed metabolic acid load contributed by Edglugate blood stored up to 5 days is of little consequence as indicated in a previous report from this laboratory.[13] During these studies of blood buffer base levels both during and following clinical perfusions, we found no significant differences between the series of patients perfused with fresh heparinized blood and the series perfused with stored Edglugate blood. In both groups of patients the decreases in blood buffer base were no greater than have been reported as resulting from nonperfusion thoracic procedures and anesthesia.[14]

Changes in certain coagulation components occurring in Edglugate blood during the first few days of storage are of particular interest.

Previously, it has been observed that disodium EDTA, particularly in excess, causes a rapid loss of plasma antihemophilic globulin and Factor V (accelerator globulin) activity.[15] More recently, Zucker and Borrelli[16] and Mustard[17] have shown that this effect of EDTA is decreased if the EDTA is kept to the minimum necessary for anticoagulation. Zucker and Borelli also found that the addition of magnesium inhibited the depression of the Factor V level. Thus besides keeping the disodium EDTA to the minimum levels

mentioned previously, we have also included a small quantity (0.15 mM) of magnesium chloride in the Edglugate mixture. Despite this addition of magnesium ion, fairly rapid inactivation of both Factor V and antihemophilic globulin occurs during the first few days of storage (Table I). These changes are more rapid than those seen in citrated blood and probably represent a price which must be paid for the use of a potent chelating anticoagulant.

Didisheim[18] has reported that all other known coagulation components are relatively unaffected by EDTA. Despite this depression of antihemophilic and Factor V activity in stored Edglugate blood, we have encountered bleeding following extracorporeal circulation in only 1 patient. While in extremis, this woman developed a potent fibrinolysin after 2½ hours of pumping during a futile effort to sustain her failing heart.

In many of our patients having open heart operations, we have carried out extensive coagulation studies both pre- and postperfusion. Pertinent data from some of these patients are given in Table IV. It will be noted that in most of these patients there was a depression of AHG and Factor V levels postperfusion. None of these patients showed any evidence of postoperative bleeding.

One patient (D) had a 99 per cent reduction in the AHG level. However, the facts that the postperfusion clotting time was normal and that he showed no bleeding tendency would indicate that the moderate fibrinolysin also found in this patient might have accounted for the falsely low AHG assay.

It is of further interest that Hoeksema, Mustard, and Mustard[19] have recently reported similar depressions in AHG levels of 10 to 80 per cent following extracorporeal circulation in patients perfused with fresh heparinized blood. This would indicate, perhaps, that like the postperfusion depression of the platelet count, the depression of AHG level is more closely related to the duration of the perfusion and any in vivo activation of the coagulation process than to the AHG content of the priming donor blood. Recently, we have had the opportunity to test the in vivo effectiveness of Edglugate plasma in a hemophiliac (AHG deficient) admitted to the hospital for elective tooth extraction. The patient's trait was severe and two siblings and two cousins had died as a direct result of their disease. This patient's AHG level was corrected and maintained with Edglugate plasma, some of which had been stored at 2° to 6° C. for periods up to 5 days. Volumes of 200 to 400 c.c. of Edglugate plasma a day were completely adequate to control this man's bleeding tendency as measured by the PTT test[5] and allow the uncomplicated extraction of 6 teeth.

As mentioned above, morphologic maintenance of formed blood elements is not equivalent to viability. The platelet counts shown in Table I are quite respectable. Platelets in Edglugate-Mg blood are in the sphere form and remain intact without clumping for many days. However, from the studies of Krevans and Jackson,[9] it is very unlikely that these platelets are hemostatically functional in vivo after more than 1 or at most 2 days' storage. In spite of this, we have seen no purpuric manifestations in any of our patients or any bleeding attributable to thrombopenia. (Tables II, IV.)

All of the patients reported in this study have been perfused by the hypothermic techniques in use at this center.[1] Because of the advantages which we feel to accrue from the combination of hypothermia and low-flow extracorporeal perfusion, we have not been willing to change our technique in order to study Edglugate blood under normothermic high-flow perfusion conditions. It is hoped that other groups evaluating this anticoagulant—preservative mixture will soon have sufficient data and experience to permit more full evaluation.

Table V summarizes the distribution of Edglugate-Mg blood for ordinary transfusion to patients on various services throughout the hospital over a 2-year period. A number of these units were distributed by the blood bank for ordinary transfusions after the heart operations for which they had been intended originally were delayed or cancelled for one reason or another. The remainder were collected during a period of 1 month when all donor blood collected in the Duke Hospital Blood Bank for all purposes was drawn into Edglugate-Mg solution. Aside from the small amount of citrated blood which was shipped to the blood bank from outside sources, every unit of blood given in Duke Hospital during this period of time was stored Edglugate-Mg blood handled through our ordinary transfusion procedures. No untoward clinical results were reported and the incidence of transfusion reactions was as low as or lower than our reaction rate with citrated blood. This portion of the study was conducted to assess the effectiveness of Edglugate blood for ordinary transfusions as compared with citrate blood. As noted in Table V, many patients received multiple spaced transfusions of this blood. Many others received large simultaneous transfusions with adequate response and without any discernible ill effects. The 945 units of Edglugate blood administered as ordinary transfusion added to the more than 600 units used in extracorporeal perfusion represents a total series in excess of 1,500 pints of Edglugate-Mg blood given to all classes of patients on the various hospital services.

Obviously, there are special conditions such as hyperkalemia, hemophilia, and the rare instances of Factor V deficiency in which citrated blood would be preferable. At the present time, we do not feel that Edglugate blood has any advantages over ACD for ordinary use, but we have found it satisfactory for the majority of patients.

SUMMARY

Until it becomes possible to maintain blood outside the body in a condition of normal homeostasis, there is no doubt that heparinized blood freshly drawn from the donor by meticulous technique is the most ideal blood for use in human perfusions.

In order to employ any substitute blood which has been stored even temporarily for this purpose, one must be willing to accept some changes in this blood as inevitable. In these studies we have attempted to evaluate both the advantages and disadvantages of an anticoagulant—preservative mixture designed

as a substitute for fresh heparinized blood. Its advantages including the possibility of having blood on hand for emergency perfusions have been outlined. Its disadvantages and limitations at the end of the 5-day permissible storage period for perfusion are increased plasma potassium content and depression of antihemophilic globulin and Factor V levels. In spite of these changes, we have had no recognizable difficulties in 81 perfusion cases employing Edglugate-Mg blood stored up to 5 days for priming the extracorporeal apparatus. We are most hopeful that continuing studies of this anticoagulant will result in further improvement of its preservation qualities for this purpose.

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(For Discussion, see page 638.)

AN AUTOMATICALLY CONTROLLED, INEXPENSIVE PUMP-OXYGENATOR

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SINCE the early reports of the successful development of extracorporeal circulation and open heart surgery,[8, 14] there has been widespread interest in refinement of techniques. Our group has directed its energies recently to the development of an inexpensive, self-controlled pump-oxygenator.

During the 10 years that we have been interested in experimental extracorporeal circulation, we have studied various types of pumps[10] as well as bubble oxygenators, screen- and disc-type oxygenators. At present, we prefer a rotating disc oxygenator which we have modified to suit our particular needs.

The apparatus consists of a rotating disc oxygenator originally suggested by Björk[1] and more recently, described by Kay and Cross[2, 3, 4, 11] and others,[16] combined with a roller-type pump. Venous blood is brought from the superior and inferior venae cavae to the oxygenator by gravity. Since a venous pump is not used, a significant source of trauma to the blood is eliminated. The pool of blood in the oxygenator serves as a venous reservoir so that the latter component is also eliminated. The discs are driven directly by a small fractional horse power motor at 120 revolutions per minute. Oxygenated blood leaves at the opposite end of the chamber and is carried by large-bore Tygon tubing to a roller pump. The pump then returns the blood to the arterial side through a filter. Excess blood in the opened, bypassed heart is collected by a suction tip attached to a second roller pump which delivers it to a combined defoaming chamber and bubble trap reservoir. From here, the blood is returned to the venous end of the oxygenator.

It has been shown by McCaughan and his co-workers[13] and others that most of the trauma to the blood removed from the opened heart results from excessive mixing of air with the blood in the suction pump. To minimize this effect, a control button has been placed on the suction handle which is pressed only when suction is desired. Thus the pump is turned on and off at the table, and the influx of air is minimized.

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The parts of the system which are in contact with blood consist of Tygon tubing, rubber, stainless steel, and silicone-coated Pyrex glass. All of the components are autoclavable, thus ensuring sterility.

CONTROLS

In most centers where cardiopulmonary bypass is used clinically, the pump-oxygenator has been operated by either a physician or a specially trained technician or group of technicians. It is usually necessary to observe several variables continuously, and make adequate adjustments during the perfusion. Among the more important factors to be observed and controlled are (1) venous pressure, (2) arterial pressure, (3) blood level in the oxygenator, (4) flow rate, (5) blood temperature, (6) replacement of blood loss, and (7) the electrocardiogram. In addition, some centers routinely monitor (8) the electroencephalogram, (9) arterial and venous oxygen saturation, and (10) blood pH and pCO_2.

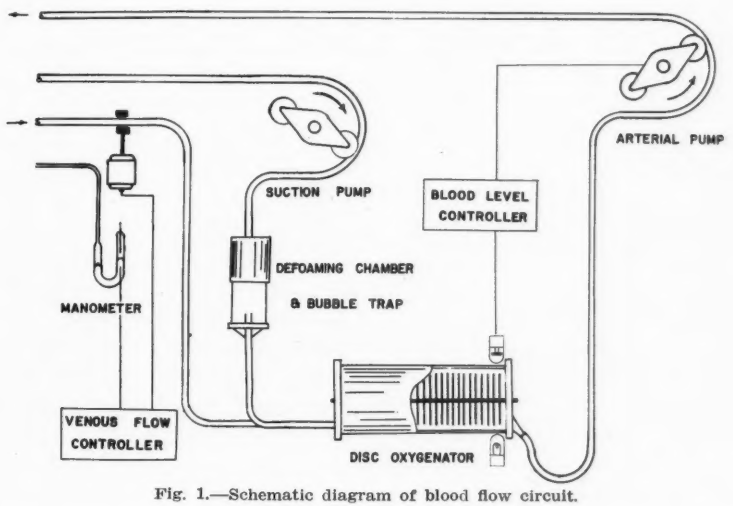

Fig. 1.—Schematic diagram of blood flow circuit.

It is generally agreed that the continuous observation and correction of the first 7 factors are necessary for a successful perfusion. By using three control systems, we are able to observe continually and maintain automatically the first 5 factors at pre-set levels. The technician is able, therefore, to direct his attention to the replacement of abnormal blood loss, under the direction of the anesthesiologist. Gibbon[8] and Kirklin[9, 12] and their associates have described the automatic control mechanisms used in the screen oxygenator which they employ.

VENOUS PRESSURE

Venous pressures are measured by passing a catheter through a superficial vein into the inferior vena cava. A sealed mercury manometer is attached to

the end of the catheter. Two electrodes are introduced into one limb of the mercury manometer and so placed to sense pressures of 10 cm. and 12 cm. of water. A motor-driven occluding clamp is placed on the main venous line between the heart and the input opening of the oxygenator chamber. Since the oxygenator is placed 75 cm. below the heart level, a greater negative pressure is developed at the opening of the venous line than can be used efficiently. A simple relay circuit is so arranged that if the venous pressure is below 10 cm. of water the motor is turned on to close the clamp $\frac{1}{8}$ of a turn, thus reducing the amount of blood removed from the venae cavae. It then waits 8 seconds to see if this adjustment is sufficient to bring the venous pressure into the "normal" range. If it is not, it will make another correction and again wait 8 seconds. If the venous pressure is between 10 cm. and 12 cm. of water (our arbitrarily selected "normal" range), the motor-driven clamp remains in a fixed position. If the venous pressure is higher than 12 cm. of water, the circuit turns on the motor-driven clamp to open $\frac{1}{8}$ of a turn, thus removing more blood from the superior and inferior venae cavae; it then waits 8 seconds and if the venous pressure has not fallen to "normal" it will then make another adjustment. This mechanism thus assures constant surveillance of the venous pressure and automatically adjusts it when indicated to ensure maintenance of normal venous pressure. Therefore, the same venous flow that would normally return to the heart is now being delivered to the pump-oxygenator.

BLOOD LEVEL CONTROL

Since reliability, autoclavability, and simplicity were the cardinal requirements in the design of the volume sensor, a means for obtaining a large output signal at useful power levels without complicated vacuum tube or transistor circuitry was sought. Methods that involve weighing the perfusion chamber, level sensors which require floats, or capacitive blood level pickup using the blood as a dielectric were rejected because of mechanical and electrical complexity.

A photoelectric blood level sensor was decided upon since it could operate outside the oxygenator chamber, eliminating cleaning and autoclaving problems. In addition, the complete generality possible with a photoelectric pickoff permits the direct application to a wide variety of oxygenator chamber designs with a minimum of modification. A light source and a light sensitive cell mounted on the outside of the oxygenator chamber are arranged so that a light beam passes through the walls of the chamber and falls upon the sensitive surface of a photocell in such a manner that changes in blood level varies the amount of the light falling on the cell. The electrical output of the cell is then used to control the speed of the arterial pump motor.

A major factor in the decision to use a photoelectric sensor was the recent advent of large area cadmium sulfide photocells of great sensitivity and capable of dissipating as much as 0.5 watt of electrical power. The output of

such a cell could easily be used to control a simple power amplifier required for the 1/8 horse power variable speed pump motor.

The cadmium sulfide cell is a photoconductive cell, that is, the electrical conductivity of the cell varies with the amount of light falling on it. As a circuit element, it behaves like a variable resistor. The type 6957 used in this system is a hermetically sealed unit in which the resistance varies from many millions of ohms when dark to a few hundred ohms when illuminated. The purpose of the photoelectric flow controller is to maintain a fixed volume of blood in the oxygenator throughout the procedure. This state of equilibrium is achieved by automatically adjusting the speed of the arterial pump which withdraws blood from the oxygenator. The pumping rate varies in response to signals from the sensor, the output of which is a function of the blood volume in the oxygenator. An increase in volume of blood in the oxygenator results

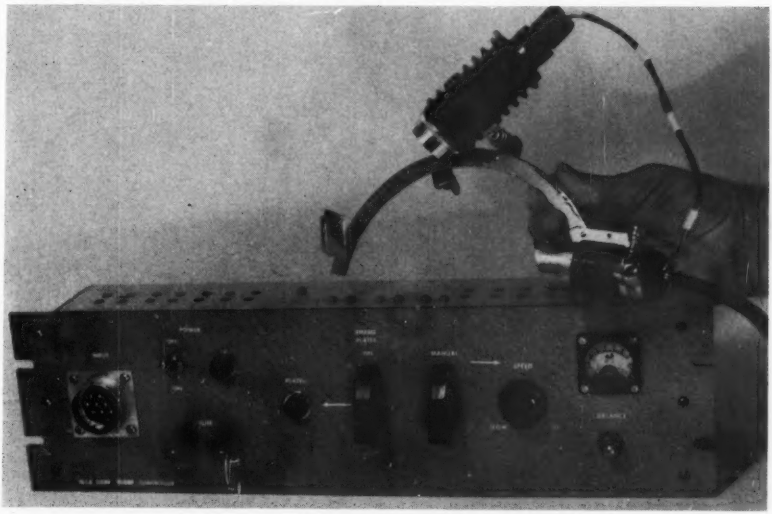

Fig. 2.—Special clamp with photoelectric cell and light source, and electronic control unit.

in an increased withdrawal pumping rate, and a decrease in volume reduces the pumping rate. The photocell is thus able to "watch" the blood level changes in the oxygenator precisely. In the 17-inch disc oxygenator, an increment of 50 c.c. of blood is detectable by the photocell. The electrical system is damped and is extremely stable. The photocell tends to select the correct pump speed continuously and maintain this speed at all times. The arterial pump output is determined by the venous return to the oxygenator. The venous return, as has been described earlier, is selected automatically to maintain venous pressures at normal levels. The blood level, then, in the pump-oxygenator is effectively locked and thus (barring abnormal blood loss from the entire system) ensures against undesirable shifts in the patient's blood volume[6, 7, 15] and automatically maintains blood pressures within normal ranges. Normal arterial

pressures assure flow rates which are consistently above 100 c.c. per kilo per minute. Thus, this one sensing device and control mechanism automatically maintains the blood in the machine at pre-set volumes, the flow rates above 100 c.c. per kilo per minute, and the arterial pressures within the normal range.

Falling arterial pressures indicate abnormal blood loss from the entire system. Blood replaced into the oxygenator will then be delivered immediately to the patient, and arterial pressure will return to the normal range. Provision is made for quickly switching the control to manual operation in case of failure,

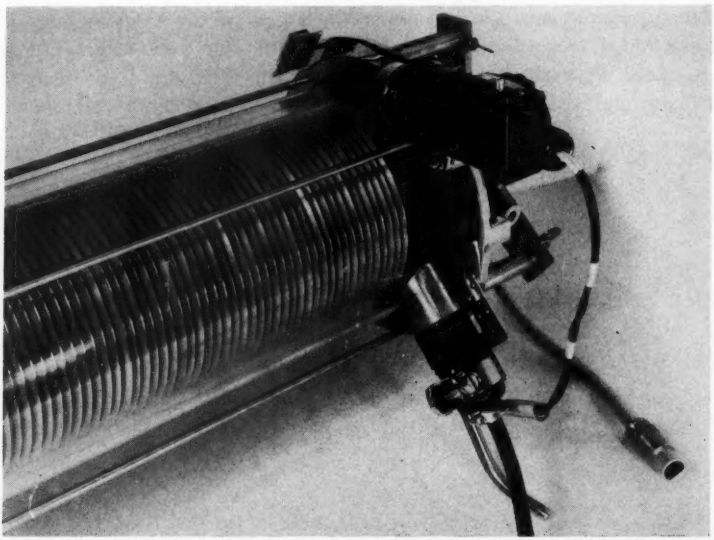

Fig. 3.—Special clamp with photoelectric cell and light source mounted on oxygenator.

by disconnecting the cell and substituting a variable resistor. The only components in the controller having finite life are two thyratrons and the excitor lamp. The thyratrons used have sufficient capacity so that if one fails, the system will continue in operation. The possibility of both thyratrons failing simultaneously is remote. Failure of the excitor lamp will cause the pump to run at full speed. In this event, the control is switched to manual operation for the remainder of the perfusion. Two excitor lamps could be built into the lamp housing for additional safety. This controller should have excellent reliability and should not be subject to sudden failure since it is simple in design and contains components that inherently have long life.

BLOOD TEMPERATURE CONTROL

It has been shown by De Wall[5] and others that it is desirable to maintain the blood in the extracorporeal circuit close to normal body temperatures. First, rapid changes in blood temperature tend to promote hemolysis of blood,

and second, oxygen is more soluble in blood at lower temperatures than at higher body temperatures. Therefore, it is possible that a saturated solution of oxygen in cooler blood in the oxygenator may come out of solution in the form of small bubbles when the blood is returned to the patient and becomes warmed. A thermistor probe is placed in a thin-walled pocket in the oxygenator chamber below the blood level. The temperature of the blood is then sensed by the thermistor and controlled by a commercially available temperature switch which turns a heater coil on and off. We have set the controller to 38° C. and are able to maintain the blood temperature within 0.5° C. The controller itself can detect changes of 1/10 of a degree centrigrade.

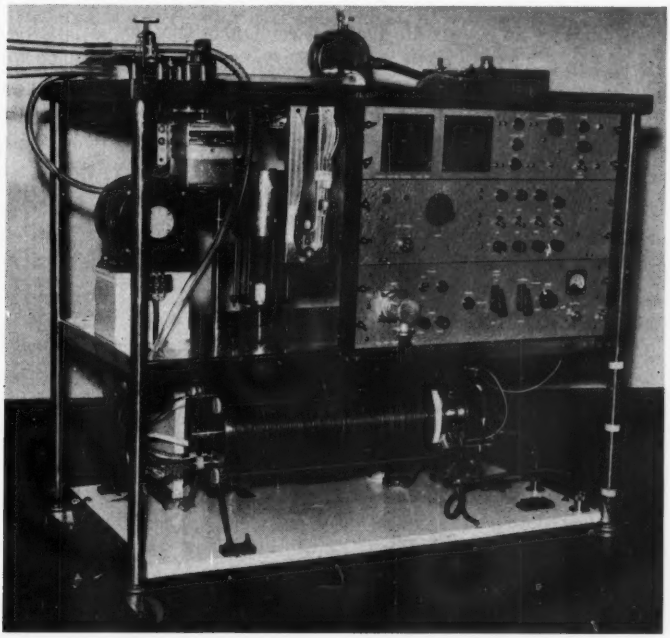

Fig. 4.—Completely assembled automatically controlled pump-oxygenator.

TECHNIQUE OF PERFUSION

The pump-oxygenator is primed with 2,500 c.c. of blood. This amount is sufficient to fill the oxygenator, the combined filter and bubble trap, the defoaming chamber, and all of the lines. Blood is circulated for a few minutes in order to be certain that all air bubbles have been removed. The arterial pump motor is turned off by a switch. The arterial and venous lines are then clamped and appropriate connections are made to the patient. To start the perfusion, the clamps are removed from the venous and arterial lines and the arterial pump motor switch is turned on. From that point on, the pump-oxygenator regulates itself. When the tourniquets around the superior and

inferior venae cavae are tightened to initiate total bypass, the increased venous return to the pump-oxygenator is automatically compensated for and all of this blood immediately returned to the patient after oxygenation. To discontinue the perfusion, one needs only to clamp the venous line. Venous return to the pump-oxygenator is then discontinued and the arterial pump will come to a stop as soon as the blood level in the oxygenator reaches its priming position.

DISCUSSION

It seems axiomatic that if a mechanism can be made to perform a given function more reliably than a human being that it should be used. A practical consideration that often enters in such a decision is the cost of such an apparatus. All of the electronic controls in our pump-oxygenator can be purchased for under $1,000.* The technician who stands by during the bypass has to be available in case of mechanical or electrical failure, in which case the pump-oxygenator can be run by manual controls. Otherwise, after the initial filling of the oxygenator with priming blood, he can devote his entire attention to replacement of unusual blood loss under the direction of the anesthesiologist.

Adjustments during the perfusion are automatically sensed and made by the machine during critical periods of change. When the perfusion is first begun, there is a tendency for the pump to overtransfuse the patient. When the venae cavae are occluded, an increased amount of blood is usually returned to the pump-oxygenator. Conversely, when the tourniquets are released, large amounts of blood can suddenly be lost from the machine. If there is unusual blood loss from the patient during the bypass, there is a tendency for blood to be lost from the pump-oxygenator. If vasopressor drugs are given, blood has a tendency to rise in the oxygenator. We feel that these abnormal shifts in blood volume are deleterious to the patient on bypass and are avoided when the blood volume in the machine is maintained at a constant level. Decreased blood level in the oxygenator decreases the efficiency of the oxygenating surface and, if the level drops low enough, may lead to air embolism. If the blood in the oxygenator rises too high, it may wet the shaft, leading to turbulence and foaming, or leak out of the shaft bearing. The apparatus that we have designed eliminates the possibility of the occurrence of these untoward manifestations.

SUMMARY

1. An improved, automatically controlled, rotating disc pump-oxygenator is described.

2. Venous pressures are continuously monitored and automatically controlled during bypass by the use of a motor-driven clamp on the venous line.

3. Blood levels, arterial pressures, and blood flows are automatically sensed and controlled with one device which is rugged, reliable, and inexpensive.

*Available from the Teca Corporation, 80 Main Street, White Plains, N. Y.

4. Blood temperatures in the oxygenator are also controlled automatically.

The authors wish to express gratitude to Mr. Percival Henry and Mr. Marco Albanese for their valuable technical assistance.

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(For Discussion, see page 638.)

AN EXTERNALLY VALVED HYDRAULIC CARDIAC SUBSTITUTE

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INTRODUCTION

IN APPLYING the techniques of extracorporeal circulation, cardiac pumps pose less of a problem in perfusions than do the oxygenator systems. Using the Sigmamotor pump, which is perhaps the most traumatic of all the commonly used machines, Lillihei and DeWall[1] express satisfaction with the amount of hemolysis produced during an average perfusion. And yet, as time goes on, and surgical bypass time increases, as more complex intracardiac defects are dealt with surgically, and as we approach the new era of medical bypass to support the failing heart, better pumps will be needed.

Four basic requirements must be met in the design of the ideal pump.[2]

1. The pump ventricle and inflow and outflow tracts should be uniform, with relatively large internal diameters.

2. All tubing surfaces in contact with blood should be mirror smooth, plastic in nature, free of turbulence, without internal valving, and be easily cleaned.

3. A variable flow from 0 to 5,000 c.c. per minute must be available which can be varied as to stroke volume and pulse rate. It should be possible to vary this flow either manually or by servomechanisms tied to either the oxygenation system or the patient's electrocardiograph.

4. Constant information should be available as to the pump volume flow and the patient's arterial and venous pressure. To ensure an accurate pump output, there should be minimal pump load sensitivity as smaller cannulas are selected and/or as peripheral resistance rises.

For practical purposes there are three types of pumps currently employed.

1. *Dale-Schuster*[3-6]—in which a ventricle is externally compressed, but not to total occlusion, and unidirectional flow is obtained by internal valving either with butterfly or ball valves, or by external valving with some form of pressure bar or point which is occlusive.

2. *Sigmamotor*[7]—in which travelling compression waves are set up in a ventricle by unidirectional rollers which are almost or completely occlusive.

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3. *De Bakey*[8]—in which travelling compression waves are produced in a ventricle by unidirectional rollers which are almost or completely occlusive.

If at some point in any of these systems there does not exist complete occlusion, the pumps become load sensitive to some degree and lose their ability to pump a constant volume of blood under all conditions of resistance. There are many perfusionists who feels strongly that it is not necessary to make their pumps occlusive. Rather than depend on a knowledge of accurate flow, they monitor systemic arterial pressure. It appears, however, that the only simple way that a pump can be constructed to be nonload sensitive is for it to be occlusive. On the other hand, as the occlusive area wiped or compressed per unit flow rate increases, so will hemolysis increase.

We have studied anew the problems relating to development of a more ideal pump and wish to present one solution to the problems just outlined. Our pump acts on an externally compressed nonocclusive ventricle of uniform Tygon tubing. The external valves act on the same piece of Tygon which is functioning as the ventricle. The tubing from the pump inlet to the outlet is uniform in diameter and without joints.

Our initial model was designed to evaluate the feasibility of some of the mechanisms proposed for a clinical pump and to provide a unit for performing hemolysis tests under varying conditions.

DESCRIPTION OF THE PUMP*

Pumping action is achieved by hydraulically squeezing a Tygon ventricle located between two mechanically actuated guillotine-type valves (Fig. 1). The valves and pumping action are synchronized so that the outlet valve opens as the Tygon is squeezed and the inlet valve opens as the Tygon returns to its normal shape. Thus, for one half cycle the pump is delivering fluid and for the other half cycle the ventricle is filling.

The hydraulic pressure, compressing the ventricle, is applied as follows: The Tygon ventricle is surrounded by a fluid-filled, annular chamber that uses a slightly larger diameter Tygon tube as its inner wall. The outside diameter of the ventricle and the inside diameter of the hydraulic chamber are essentially the same. Fluid is delivered to and taken from the annular chamber by the mechanical actuation of a rubber diaphragm located on an auxiliary chamber which is hydraulically connected to the annular chamber. The two chambers form a closed, sealed hydraulic unit with no possibility of leakage into the blood containing ventricle. A positive hydraulic action in the annular chamber is assured that is directly proportional to the mechanical action on the diaphragm of the auxiliary chamber. The mechanism is arranged so that at no time does the Tygon ventricle become occlusive.

Valving action is achieved by occlusively squeezing the ventricle tubing with transverse rods, ¼ inch in diameter, externally located 1 inch from the ends of the annular chamber. The valves are actuated through lever arms connected

*Manufactured by The United Precisioneers Inc., Calabasas, Calif.; distributed by The Mark Co., Randolph, Mass.

to cams located on the main-drive shaft. The eccentric, which operates the diaphragm actuating mechanism, is also on the main-drive shaft, thus ensuring positive synchronization between the valves and pumping action.

The pump is driven by a model M143 Zero-Max variable speed drive and motor. A belt with a three-to-one pulley reduction is used, giving available pulse rates of zero to 130 pulses per minute. The Zero-Max speed control is used to vary the pulse rate. A mercury switch, to eliminate sparking, is used for the main power switch. Separate control knobs adjust the pulse rate and the stroke volume independently of one another. The flow rate can be varied from zero to full flow by changing the pulse rate and/or by changing the stroke volume while the pump is stopped or in operation.

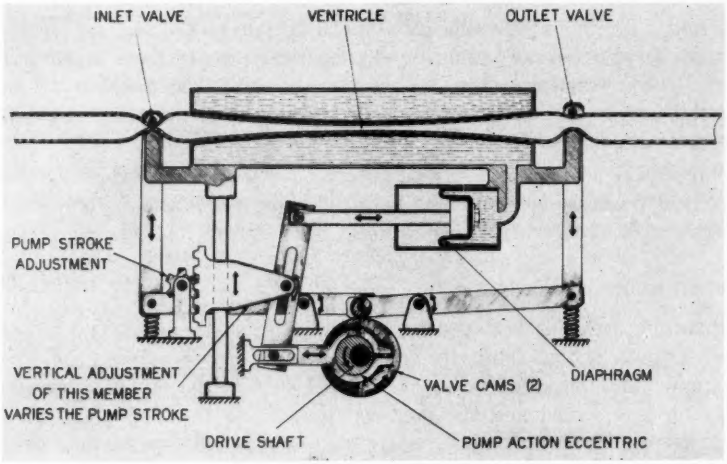

Fig. 1.—Diagrammatic sketch of the hydraulic pump principle. Note that the drive shafts actuating the hydraulic cylinder and the arms to the guillotine valves are synchronous and mechanically linked.

Using a 12-inch ventricle length with a ⅛ inch wall and an internal diameter of ¾ inch, a maximum flow of 5,800 c.c. per minute at a pulse rate of 114 was obtained. This flow can be easily increased by using a larger ventricle. The pump is self priming and is essentially not load sensitive. It has been run continuously in one test for over 50 hours at 100 pulses per minute using the same ventricle, without producing noticeable damage to the Tygon tubing and without altering the pumping characteristics.

A second pump has been designed and tested using a mechanical pressure bar instead of hydraulic fluid to compress the ventricle. Since the ventricle is not occluded by the pressure bar and all other aspects of the pump were kept constant, we could find no essential difference in the performance between the hydraulic and mechanical ventricles.

A third pump, which is the clinical unit, was prepared utilizing identical but refined principles outlined in this paper but with a mechanical compression bar acting on the ventricle.

TEST METHOD

In order to evaluate the described pump, comparative hemolysis tests were concurrently performed with De Bakey,* Sigmamotor, and the UPI pumps. Freshly drawn, heparinized dogs' blood from several animals was premixed in a plastic container from which equal volumes were taken for each of the test pumping circuits. The blood was placed in identical plastic test chambers and circulated through identical circuits until each pumping circuit was free of air. Control bloods were taken after the circuits were filled and free of air; thereafter the pumps were operated for varying test periods as required. For each study, the test chambers were kept of uniform size, shape, and position and all adapters and orifices were of uniform size so that all tests and pumps can be directly compared.

Plasma hemoglobin, proteins, fibrinogen, and platelets were monitored during the tests. The results obtained from electrophoretic protein determinations were so equivocal as to exclude them from presentation. Likewise, the heparin effect rendered platelet and fibrinogen determinations so inaccurate that they had no comparative validity in our study.

We relied, therefore, on plasma hemoglobin determinations as our most accurate criterion of blood damage. The determinations of plasma hemoglobin were done spectrophotometrically using the Beckman DU spectrophotometer with readings at 540 and 570 mμ, the results being averaged.

The following studies were accomplished: (a) pulse wave and pressure recordings were taken proximal and distal to each ventricle and also within the UPI pump ventricle, (b) load sensitivity determinations, and (c) hemolysis with both open lines and with constriction. Our basic pump principles were then reevaluated and a clinical pump designed and fabricated.

RESULTS

Pressure Characteristics.—Many combinations of flow rate and cannula size were tested; however, data are presented herein only for combinations that are representative of most common conditions under which pumps would be operating.[10]

A comparison of pressure wave forms of all three pumps at a flow rate of 3,000 c.c. per minute, pumping through a 0.25 inch constriction, is presented in Fig. 2. Pressures were obtained from each pump distal and proximal to the ventricles; in addition, it was possible to obtain ventricle pressures in the UPI pump.

De Bakey: The peak pressure range was +50 mm. Hg to −75 mm. Hg at 48 pulse rate. The inlet line wave form was sinusoidal and damped over the duration of the cycle with a negative mean pressure. The outlet line wave form was a very shallow sine wave superimposed on the mean positive pressure. During only a small part of the cycle is the outflow pressure less than zero which indicates that this pump is, in a sense, the least pulsatile of the three studied.

*Designed and kindly furnished for tests by Peter F. Salisbury, M.D.

Sigmamotor: The pressure range was +170 mm. Hg to –160 mm. Hg at 125 pulse rate. The inlet wave form was a single sine wave with the positive pressure shape distorted due to the action of the finger cams. The outlet wave form was a single sine wave with the entire wave distorted by a higher frequency smaller amplitude wave also produced by the action of the finger cams.

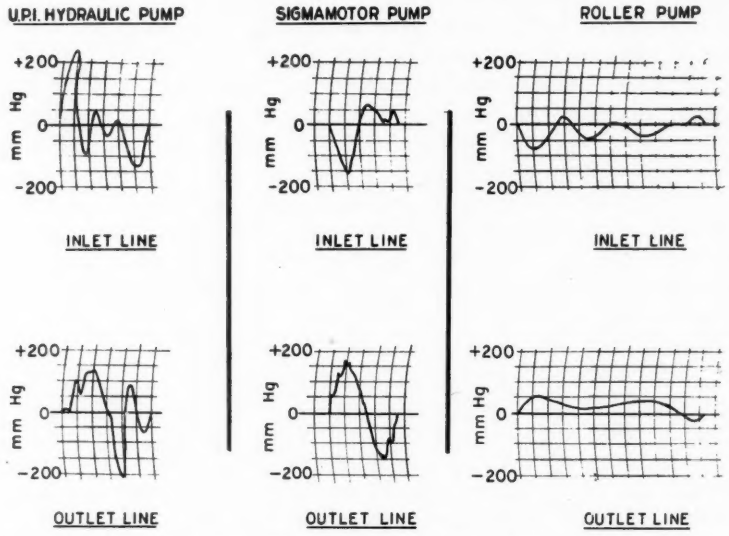

Fig. 2.—Comparative ventricle pressure wave forms for single cycles at 3,000 c.c./min. flow with outlet line constricted to 0.250 inches in diameter.

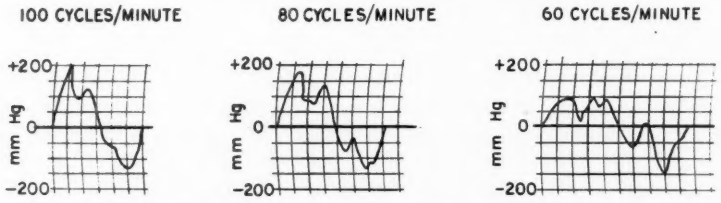

Fig. 3.—Comparative wave forms of the UPI pump for single cycles at 3,000 c.c./min. at pulse rates of 60, 80, and 100 cycles per minute. Note that the slower the pulse rate the lower is the intraventricular pressure.

UPI: There was a pressure range of +250 mm. Hg to –210 mm. Hg at 100 pulse rate. The inlet and outlet line wave forms were essentially similar. The pressure wave distortion could have been due to the elastic characteristics of the Tygon tubing which was free to absorb and release energy in the ventricle. Under the test conditions this pump developed the highest measured pressures. Since the ventricle fills during one half the cycle and pumps during the other half, a higher pressure is required than in either of the other two pumps at near the maximum pulse rate. However, the most adverse pump system pressures encountered were within the upper limits of the physiologic range.

The UPI pump ventricle pressures at 3,000 c.c. per minute, pumping against a 0.25 inch restriction at pulse rates of 60, 80, and 100 per minute are given in Fig. 3. It was found that as the pulse rate increased there was a parallel increase in intraventricular pressure. In considering two identical total volume flows per unit time, each with a different pulse rate, the higher pulse case requires higher fluid accelerations and, therefore, results in higher peak pressures. This effect is clearly shown in Fig. 3.

Load Sensitivity and Pressure Response to Load.—When all three pumps were set just occlusive, there was little difference in drop of minute volume output under constriction. The UPI pump showed the greatest load sensitivity of the three pumps tested but the maximum drop in flow for a 3/16 inch cannula at 3,000 c.c. per minute was less than 3 per cent (Table I).

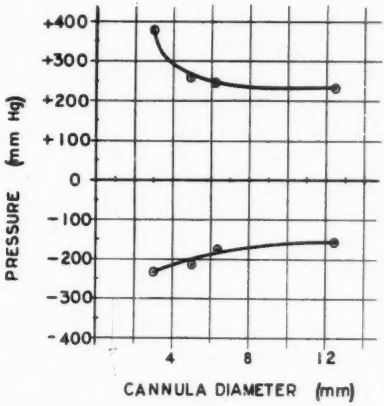

Fig. 4.—UPI pump ventricle pressure vs. cannula size at 3,000 c.c./min. flow rate and 100 cycles per minute pulse rate.

TABLE I. LOAD SENSITIVITY COMPARISON FOR VARIOUS TYPE PUMPS*
(PER CENT DROP IN FLOW AT 3,000 C.C./MIN.)

RESTRICTION (CANNULA I.D.)	UPI PUMP (HYDRAULIC) (% DROP IN FLOW)	SIGMAMOTOR PUMP (% DROP IN FLOW)	ROLLER PUMP (% DROP IN FLOW)
None	0.00	0.00	0.00
¼ inch	1.50	1.00	0.50
3/16 inch	2.90	1.60	0.75
⅛ inch*	6.60	2.45	2.00
Pulse rate	100	126	48

Load Sensitivity: At flow rates of 1,000 c.c./min. with a ⅛ inch cannula and at flow rates of 3,000 c.c./min. with a ¼ inch cannula, all pumps being occlusive, there was no appreciable drop in the flow rates from pre-set levels.

**NOTE:* The work of Reference 2 indicates that for flows of 3,000 c.c. per minute cannulas should be no less than ¼ inch internal diameter.

Since the UPI pump ejects fluid during only one half of each pumping cycle, its pumping characteristics are more sharply pulsatile than either the De Bakey or the Sigmamotor pumps. A family of curves were studied (Fig. 4 being representative) of intraventricular pressures produced while pumping through cannulas of gradually decreasing inside diameter at constant minute

volume. This characteristic might suggest the use of a simple pressure surge chamber to reduce peak pressures for extra high flow rates and small diameter cannulas.

The safe lower limits of cannula size were taken from the work of Clowes and his associates[11] in which it was shown that the upper limits of safe flow were: 3 mm. cannula, 650 c.c. per minute; 5 mm. cannula, 1,800 c.c. per minute; and 8 mm. cannula, 3,400 c.c. per minute. It was found that the intraventricular pressures of the UPI pump did not exceed physiologic limits when examined under these conditions.

The flow rates in the De Bakey and Sigmamotor pump are primarily dependent on pulse rate. In the case of the De Bakey pump, pulse rates approach a normal value for high flow rates and are quite low for smaller minute volumes.

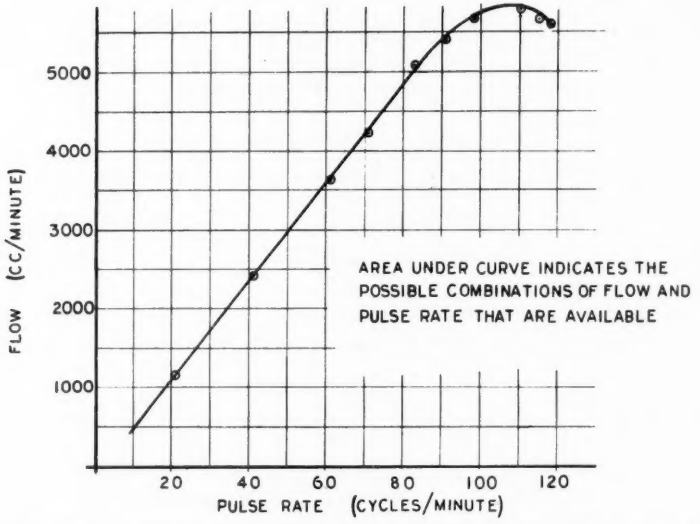

Fig. 5.—Illustrates the combinations of flow rates and stroke adjustment that are available with the UPI pump.

On the other hand, the Sigmamotor pump develops a pulse that is very rapid at high flow rates. Between 0 and 3,000 c.c. per minute, the UPI pump is capable of functioning at any selected pulse rate between 50 to 120 cycles per minute (Fig. 5). The pulse ranges as a function of volume flow rate for all three pumps can be seen in Table II which clearly indicates the versatility of pulse rate for the UPI pump.

TABLE II. PULSE-FLOW CHARACTERISTICS FOR VARIOUS TYPE PUMPS

TYPE OF PUMP	PULSE RANGE AT FLOW RATE OF		
	1,000 C.C./MIN.	3,000 C.C./MIN.	4,500 C.C./MIN.
De Bakey	20	48	74
Sigmamotor	45	125	180
UPI (hydraulic)	19 to 120	50 to 120	75 to 120

Hemolysis.—All three pumps were tested under two conditions: (a) at flow rates of 3,000 c.c. per minute with no line constriction and with a simple plastic reservoir in the circuit (the total system volume circulated was 800 c.c.); (b) at flow rates of 2,400 c.c. per minute with a 0.25 inch I.D. cannula restriction in the line (the circuit included a debubbling chamber of stainless steel sponge and contained a total system volume of 1,000 c.c.).

Although a flow rate of 3,000 c.c. per minute could be achieved by the UPI pump in a variety of ways, that is, with a single or double ventricle and at any pulse from 50 to 120 cycles per minute, we chose conditions which would seem to be as unfavorable as possible. Therefore, the UPI pump was tested with a single ventricle and at the higher pulse rates.

The UPI hydraulic pump was considerably less traumatic to blood than the other two pumps tested. Under conditions of no line constriction, the UPI pump was twofold less traumatic to blood than the De Bakey and four and a half times less traumatic to blood than the Sigmamotor pump. When a line constriction was placed in the circuit, the difference was even more marked. The UPI pump was fourfold less traumatic than the De Bakey and twenty-seven times less traumatic than the Sigmamotor pump (Table III).

TABLE III. CIRCULATING TIME 2 HOURS*

	PUMPS DELIVERING 3,000 C.C./MIN. INTO SIMPLE RESERVOIR (TOTAL SYSTEM VOLUME 800 C.C.)			PUMPS DELIVERING 2,400 C.C./MIN. THROUGH A ¼ IN. CONSTRICTION INTO DEBUBBLING CHAMBER (TOTAL SYSTEM VOLUME 1,000 C.C.)		
TYPE OF PUMP	MG. % FREE HBG.	TOTAL GM. FREE HBG.	INDEX OF HEMOLYSIS	MG. % FREE HBG.	TOTAL GM. FREE HBG.	INDEX OF HEMOLYSIS
UPI	31	0.248	0.069	14	0.140	0.043
De Bakey	62	0.496	0.138	60	0.600	0.173
Sigmamotor	144	1.152	0.320	384	3.840	1.334

*Index of comparative hemolysis between the UPI, De Bakey, and Sigmamotor pumps operating under identical conditions. Note that the UPI pump causes from 2 to 27 times less hemolysis than the other two pumps studied. Index of Hemolysis = mg. free Hbg. produced per 100 c.c. of flow.

To determine the effect of varying the pulse and flow rates of the UPI pump, 800 c.c. of freshly drawn dog blood was circulated through a simple reservoir for a period of 1 hour. Studies were made at pulse rates of 60, 80, and 100 cycles per minute and at volume flows of 1,500, 3,000, and 4,500 c.c. per minute. Inspection of Table IV shows that there was little change in the

TABLE IV. ONE HOUR CIRCULATING TIME—800 C.C. CIRCULATING VOLUME*

TYPE OF PUMP	FLOW RATE (C.C./MIN.)	TOTAL FLOW (C.C.)	PULSE RATE (CYCLES/MIN.)	HBG. CONCENTRATION AFTER 1 HOUR (MG./100 C.C.)	TOTAL FREE HBG. (MG.)	INDEX OF HEMOLYSIS (MG./100 C.C. OF FLOW)
UPI	1,500	900×10^2	80	13	104	0.116
UPI	3,000	$1,800 \times 10^2$	60	13	104	0.058
UPI	3,000	$1,800 \times 10^2$	80	13	104	0.058
UPI	3,000	$1,800 \times 10^2$	100	12	96	0.053
UPI	4,500	$2,700 \times 10^2$	80	18	144	0.053
De Bakey	3,000	$1,800 \times 10^2$	48	25	200	0.111
Sigmamotor	3,000	$1,800 \times 10^2$	125	102	816	0.453

*Index of comparative hemolysis of the UPI pump at a sampling of different pulse and flow rates with no line constriction. Hemolysis is almost negligible.

Index of Hemolysis under different conditions and, under all conditions tested, the UPI pump was less traumatic to the circulating blood than the other two pumps under similar conditions.

Clinical Pump.—On the basis of these laboratory studies a clinical pump was designed and fabricated (Fig. 6).

This model consists of three parallel ventricles with pumping strokes 120 degrees out of phase with each other. Three Tygon tubes are held in place by an easily removable cover. The pumping and valving action is achieved by members acting against the Tygon tubing from the under side, compressing it against the cover.

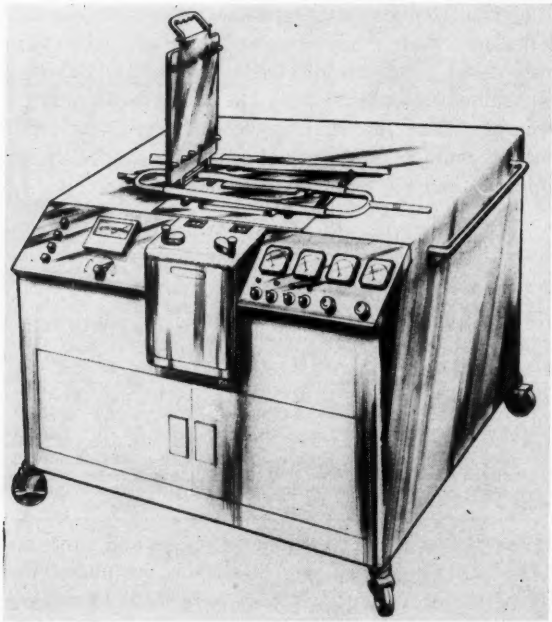

Fig. 6.—Clinical version of UPI pump with mechanical linkage, nonocclusive pressure plates, and occlusive guillotine pressure-valve bars mounted in a console with related ancillary equipment.

The ventricles are compressed by mechanical pressure bars and as was pointed out earlier, there was no difference noted in performance between nonocclusive mechanical and hydraulic compression. The valving action is the same as described in the experimental model.

A single direction clutch has been added to permit emergency hand cranking in the event of power failure. Small hand wheels control the length of the pressure plate travel against the ventricle; turning the wheel varies the flow per ventricle from zero to 4,000 c.c. per minute. The two main ventricles are controlled by a single wheel so that they may be connected in parallel for high

flow rates up to 8,000 c.c. per minute. The other ventricle is controlled by the second hand wheel and may be used independently for either suction or coronary perfusion. Other basic controls consist of the usual electrical circuits and a pulse control adjustment for the variable speed drive.

This design has, as an integral part of its construction, provision to tie servomechanisms into the various components which can make the pumping action automatic within the system or synchronous with the patient's own cardiac output. This ancillary equipment, monitoring devices, and servomechanisms will be the subject of another communication.

CONCLUSIONS

We found that external compression without occlusion on a ventricle would appear to be the least traumatic method of pumping blood that we studied. Such a system requires valving at each end of the ventricle and the simplest arrangement with the least occluding surface is the pressure bar, guillotine valve. We have utilized mechanical linkages and control methods which makes the entire pump more reliable than either hydraulic or electronic linkages and/or controls.

This pumping mechanism is virtually fail-safe, trouble free, and is at least two to four times less traumatic to blood than other pumps studied. Pulse rate and stroke volume are individually variable. The pump is so designed that it may be incorporated in combination with servomechanisms.

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(For Discussion, see page 638.)

PHYSIOLOGIC P-WAVE CARDIAC STIMULATOR

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In 1862, Walshe[1] suggested the possibility of external control of the cardiac rate. This suggestion lay practically dormant until Zoll and co-workers,[2] in 1953, described the use of an artificial external cardiac pacemaker for treatment of the Stokes-Adams syndrome.

Analysis of the fatalities following intracardiac surgery, especially the repair of interventricular septal defects, utilizing extracorporeal circulation revealed that atrioventricular dissociation was one of the major problems leading to death in the postoperative period. Detailed studies on the relation of the bundle of His to the septal defect yielded some helpful suggestions as to the placement of sutures to avoid the conduction system but did not negate the problem.

Weirich,[3] working at the University of Minnesota, reported in 1957 the use of a timed external pacemaker functioning through a ventricular electrode to stimulate the heart through the critical postoperative period. Many others have utilized this method to treat postsurgical heart block.

We have been interested in the same problems but have felt that a more physiologic control of ventricular rate would be desirable and thus cardiac output would adjust automatically to such variations as temperature elevation, ambulation, and exercise in the postoperative period.

Feeling that the inherent mechanism to control cardiac rate in the intact individual would be difficult to improve on, we have constructed an instrument which utilizes the auricular p wave to trigger a ventricular stimulator and thus produce a sinus rhythm through an extracorporeal system substituting for the A-V node and bundle of His.

DESCRIPTION OF THE APPARATUS

The basic component of the artificial system is a modification of a muscle potential amplifier originally developed by Montgomery at this institution and designed to control an artificial ventilatory device.[4, 5, 6] This control unit is

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sensitive to impulses as low as 0.5 microvolt and contains satisfactory electronic filters to block extraneous impulses arising from external magnetic fields and artifacts. The control unit amplifies the electrical potential of auricular contraction picked up by an insulated wire lead sutured to the auricular myocardium. The amplifier processes these potentials to produce a control voltage corresponding in time with the p wave.

In operation this control voltage is modified to trigger a monostable multivibrator. The first stage vibrator acts as a variable delay unit with an adjustment from 0 to 1 second. This variable allows adjustment of the delay to correspond to the normal conduction time of the bundle of His (0.18 second). The amplified p wave is also used to trigger the sweep of a monitor oscilloscope for either the action of the amplifier or the stimulator output. The output of the delay circuit is fed into another monostable multivibrator which is capable of producing a square wave output of variable duration with a range of 0 to 1 second. This duration adjustment is usually maintained at a little less than 0.1 second which is the time normally required for stimulation of the ventricle.

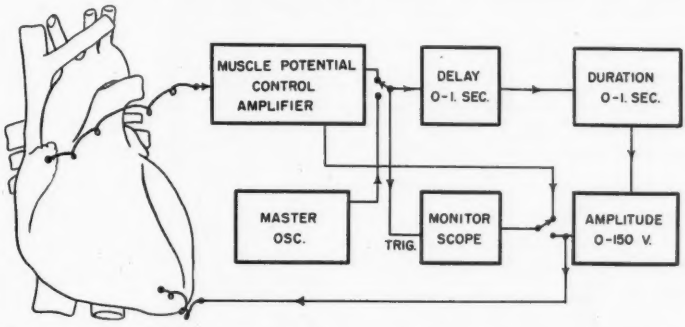

Fig. 1.—Block diagram of the p-wave cardiac stimulator showing areas of electrode insertion.

A variable output of from 0 to 150 volts is available on the unit and this can be controlled by selecting the minimal stimulus to which the ventricle will respond. (The standard Grass model S4E laboratory stimulator fills all the requirements set forth and functions smoothly as the stimulator component of the circuit.) A master oscillator is included as an emergency trigger source in case of difficulty arising with the auricular pickup or in case of complete asystole (Fig. 1).

METHODS

Unselected mongrel dogs of 6 to 16 Kg. in weight were prepared under aseptic conditions. A right thoracotomy was performed and the bundle of His was identified by passing an insulated needle through the right auricular wall into the septum. The conduction system was destroyed by an electrocoagulation technique (to be published). After satisfactory idioventricular rhythm was established, braided wire electrodes were attached by means of mattress sutures

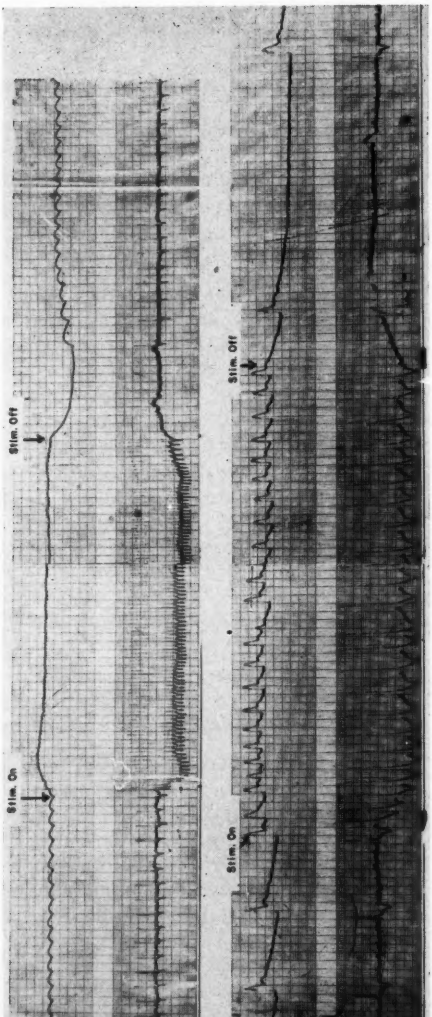

Fig. 2.—Two segments of a tracing showing the application and removal of the p-wave stimulator. The upper segment shows the mean arterial pressure rise with stimulation and the lower segment shows individual contractile pressure changes.

to the right auricle and near the apex of the ventricles. These wires were brought out of the chest cavity and the distal ends buried in the subcutaneous tissue.

Measurements of the arterial pressure, pulse rate, venous pressure, and tracings of the electrocardiogram and electroencephalogram were made pre- and postoperatively and were repeated when periods of stimulation were carried out. Cardiac outputs using the indigo carmine dye technique were done on some animals pre-block, post-block, and post-stimulation.

After a period of time elapsed to allow for healing from the operation, the leads were exposed under local anesthesia and p-wave stimulator attached. The animals could be stimulated for any length of time and, if desired, the leads put back in the subcutaneous tissue and the wound closed for later stimulation.

Fifty-nine animals had an attempt at destruction of the bundle of His. Thirty-nine of these animals developed a complete and permanent block and were available for subsequent stimulation.

RESULTS

Utilizing the group of animals previously described, approximately 400 hours of stimulation have been carried out. The duration of stimulation has varied on individual dogs from 30 minutes to 72 hours. Long-term stimulation has been possible with the production of a stable electrocardiogram and only minimal changes necessary in the settings of the stimulating mechanism.

Table I shows the average changes in pulse rate, peripheral arterial pressure, venous pressure, and cardiac output that occur prior to destruction of the bundle of His, after block and the development of an idioventricular rhythm, and during stimulation of the ventricle by the p-wave triggered stimulator.

TABLE I

	PREOP.	POST-BLOCK	STIMULATION
Average pulse rate per minute	126	62	126
Average arterial pressure (mm./Hg)	122/70	108/60	126/72
Average venous pressure	6	12	5
Average cardiac output Index (l/M.^{2})	2.25	1.24	2.23

The marked decrease in pulse rate, average fall of 14 mm. Hg in systolic arterial pressure, 100 per cent increase in caval venous pressure, and 55 per cent reduction in cardiac output are obvious. During stimulation these values quickly revert to normal (± 5 per cent) (Fig. 2).

We feel the decreased cardiac output and increased venous pressure to be the most deleterious effects of the idioventricular rhythm. Mowlem and Campbell[7] have recently reported the acute changes occurring with induced heart block but found that changes affecting the left heart (left atrial pressure and left ventricular end-diastolic pressure) rather quickly reverted to normal. This rapid return to normal does not hold true in a chronic situation with respect to venous pressure and cardiac output. Sixty per cent of our animals

which survived 3 months developed massive ascites and other evidence of right ventricular failure. These changes respond slowly to digitalis and paracentesis.

In attempts to evaluate the advantages of the p-wave stimulator we have studied cardiac outputs that could be obtained using conventional timed stimulators acting through a ventricular electrode. The results of these tests are presented in Table II. It seems that with persistence and frequent measure-

TABLE II*

	PRE-BLOCK INDEX	BLOCK INDEX	STIMULATION INDEX
A. P-Wave Stimulator	2.94	1.47	2.92
B. Conventional Timed Stimulator			
Rate *Voltage*			
48 8.2			1.15
90 8.6			2.74
144 8.6			3.0
152 9.0			3.47

*Cardiac indices are stated in liters per square meter of body surface.

ments of cardiac output that one might be able to arrive at a normal output with a mechanically timed stimulator. We were not, however, able to do this with any degree of accuracy. Certainly a return to essentially normal physiologic measurements is more quickly and easily made with the auricle triggering the stimulator.

DISCUSSION

This is a preliminary report on one of the approaches to extracardiac stimulation. We know of no other such unit available. Folkman and Watkins[8] have reported the use of a transistor unit to amplify the auricular p wave and use this to trigger the ventricle but this has certain disadvantages. Among these objections are the poor electrical characteristics of the p wave for stimulation, lack of a delay circuit (p-r interval), and long duration of the stimulus.

The unit described herein has proved to be simple to use and takes advantage, except for the muscle potential amplifier, of commercially available circuits. As the unit now stands it is bulky and not very mobile. These disadvantages can be obviated, however, by transistorizing the circuits and work along this line is progressing.

One problem which still must be answered is the duration of time one can stimulate through a single set of implanted electrodes. At the present time, 6 to 8 weeks of constant stimulation will cause enough fibrosis to prevent adequate stimulation. This period can be lengthened by intermittent stimulation. The solution to this problem must be reached, however, since, with direct electrodes, shocks in the range of 4 to 12 volts for stimulation are well tolerated by the heart and the remainder of the organism for long periods of time. If one relies on external cardiac pacemaking through the intact chest, voltages may go as high as 180 volts (Zoll, unpublished). Electric shock in this range is not only very uncomfortable for the patient but the individual also suffers the effects of a tonic seizure with each ventricular contraction.

SUMMARY

1. A p-wave triggered, ventricular, extracardiac stimulator has been described which experimentally produces physiologic hemodynamic changes.

2. This unit has been evaluated on a large group of experimental animals and has proved safe and effective.

3. The decreased cardiac output and the elevated venous pressure appear to be the most important functions to consider in treating temporary or permanent heart block.

4. Some of the difficulties associated with extracardiac ventricular stimulation are discussed.

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(For Discussion, see page 638.)

"TRANQUILIZATION" OF THE HEART WITH THE ATARACTIC DRUGS

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CARDIAC arrhythmias continue to pose a hazard to patients subjected to cardiac surgery. The incidence has been lowered by an understanding of the importance of maintaining normal physiologic conditions, and yet there are many instances in which the pathologic anatomy to be corrected has set the stage for possible cardiac irregularities. Quinidine and Pronestyl, drugs widely used for the medical control of arrhythmias, have side effects which make their use undesirable before or during surgery. With the observation in our laboratory that certain antihistaminic and ataractic (tranquilizer) drugs apparently exert a stabilizing or "tranquilizing" effect on the heart,[1] and in view of reports in the literature suggesting clinical usefulness of certain ataractic drugs in cardiac arrhythmias,[2, 3, 4] this study was begun to see if the ataractic drugs could convert ventricular fibrillation into a normal sinus rhythm. Subsequently, questions were raised regarding the possible effects of these drugs on the normally beating heart, and if any protection might be afforded against the occurrence of ventricular fibrillation.

The study and the results reported here are regarded as preliminary observations of work in progress. Nonetheless, these findings appear to be of such interest that an initial report seems warranted.

METHOD

An isolated canine heart, biologically supported by a donor dog, was utilized as the preparation for study. The isolated heart was procured from a dog via a right thoracotomy under pentobarbital anesthesia. The heart was arrested by injecting 20 ml. potassium citrate (2.5 per cent) into the coronary arterial circulation after the dog had been heparinized (3 mg. per kilogram). After removal of the heart, the proximal end of the transected thoracic aorta was cannulated to permit retrograde perfusion of the coronary arteries. The brachiocephalic artery was cannulated to monitor the perfusion pressure and other aortic branches were ligated. Electrocardiographic tracings were recorded

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from surface electrodes, and the temperature was determined by a thermistor probe immersed in the blood after it had been ejected from the isolated heart into a receiving funnel.

The temperature was maintained at 85° to 98° F. by heat from infrared lamps adjacent to the isolated heart, and with a heating pad under the supporting dog.

Blood was delivered from the femoral artery of the supporting dog to the isolated heart via tubing placed through an occlusive Sigmamotor pump. Flow rates were then governed by adjusting the pump so that the pressure in the isolated heart preparation was within normal limits. Blood was then collected

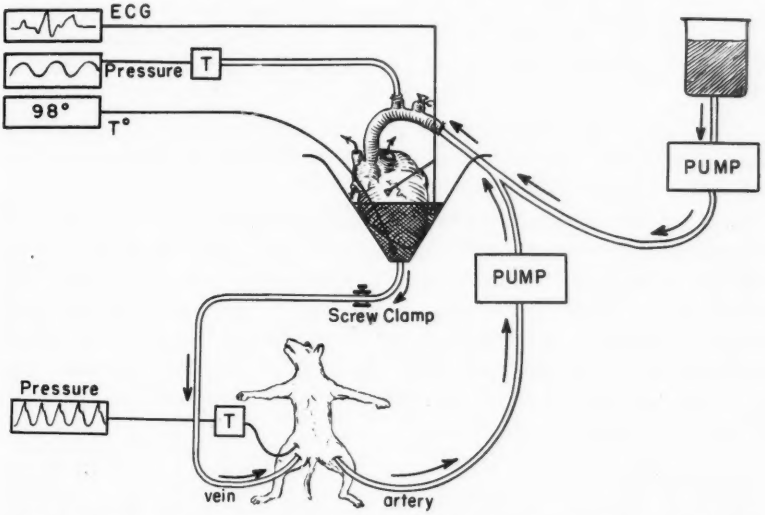

Fig. 1.—Diagrammatic representation of the biologically supported isolated heart preparation. Arterial blood from the supporting dog is pumped, in retrograde fashion, into the thoracic aorta. After passage through the heart, blood is collected and returned to the dog via the femoral vein. Continuous monitoring of the isolated heart electrocardiogram, pressure, and temperature, in addition to the pressure of the supporting dog, are depicted. Drugs to be assessed are added from a reservoir into the arterial line by another occlusive pump.

and returned to the femoral vein by gravity. Respirations of the supporting dog were maintained with oxygen administered by intermittent positive pressure via an endotracheal tube. Arterial pressure was continually monitored on an oscilloscope.

Drugs to be tested were added to the arterial limb of the circuit just proximal to the isolated heart by means of a second occlusive Sigmamotor pump, adjusted to deliver 100 to 125 ml. per minute.

Spontaneous cardiac activity in the isolated heart was usually established within an hour of elective cardiac arrest. The type of cardiac rhythm was controlled by means of electric shocks. If normal sinus rhythm was desired, one shock of 90 volts was used; if ventricular fibrillation was desired, repeated shocks

of 3 volts were used. Duration of the shock was 0.1 second. Once reproducible responses were achieved, ventricular fibrillation was induced and the preparation was ready for study.

Five hundred milliliters of normal saline was first administered over a period of 4 to 5 minutes as a control. Then, by means of shocks of voltages as described, the heart was put into a normal sinus rhythm, then to ventricular fibrillation, repeating several times, again to ensure validity of the preparation. Ventricular fibrillation was then again induced. The drug to be tested was then added. For the ataractic drugs, the initial concentration was 50 mg. in 500 ml. saline (or the equivalent), or multiples thereof in case more drug was required. With quinidine, 80 mg. or multiples thereof were used. If the heart was still in fibrillation at the end of this infusion, additional mixtures were prepared and administered. When conversion from ventricular fibrillation to normal sinus rhythm had taken place, the volume given and the time for administration were noted.

Drug-induced protection against ventricular fibrillation was presumed to be present if the same stimuli, which repeatedly caused fibrillation previously, failed to do so after administration of a drug.

This report concerns forty-two experiments which were performed after the techniques and protocol were standardized. The following drugs have been studied: hydroxyzine (Atarax*) in 15 experiments, prochlorperazine (Compazine†) in 4, promethazine (Phenergan) in 2, reserpine (Serpasil) in 1, promazine (Sparine) in 1, trifluoperazine (Stelazine†) in 8, chlorpromazine (Thorazine†) in 2, perphenazine (Trilafon‡) in 5, and, for comparison, quinidine. (For the sake of simplicity the proprietary names of these agents are used rather than the generic names.)

RESULTS

1. *Effects of Drugs on the Heart in Ventricular Fibrillation.*—

Each of the ataractic drugs used proved to be capable of converting the heart in ventricular fibrillation to a normal sinus rhythm. Of the 38 hearts so tested, 33 were thus converted and 5 were not. The dosage required varied widely and did not correlate with any of the measured variables. In the remaining 4 dogs, quinidine similarly was effective in restoring a regular beat to the fibrillating heart and with a time-dosage range comparable to that of certain ataractic drugs.

The results are tabulated in Table I.

Two distinct types of electrocardiographic patterns were observed during the conversions. In some instances, the amplitude of the ventricular fibrillation became progressively lower until a state of asystole ensued. From asystole, recovery to normal sinus rhythm regularly followed. In other instances, the intermediary stage of asystole was not observed, there being a direct conversion

*Kindly supplied by J. B. Roerig & Company, New York, N. Y.
†Kindly supplied by Smith, Kline & French Laboratories, Philadelphia, Pa.
‡Kindly supplied by Schering Corporation, Bloomfield, N. J.

TABLE I. ADMINISTRATION OF ATARACTIC DRUGS TO ISOLATED HEARTS IN VENTRICULAR FIBRILLATION

	CONVERSION VF* TO NSR†	DOSAGE REQUIRED (MG./MIN.)		DOG WEIGHTS (LB.) SUPPORTING DOG	DOG WEIGHTS (LB.) HEART DOG	SUBSEQUENT PROTECTION VS. V.F.*
Atarax	+	33	3	38	31	+
	+	750	80	75	38	+
	+	65	27	43	21	
	+	15	1	40	29	
	0	550	89	43	31	
	+	100	18	38	36	+
	0	250	25	38	32	
	0	300	66	40	23	
	+	50	7	50	20	
	+	115	14	52	27	
	+	100	14	45	26	
	+	40	3	48	24	+
	+	15	2	63	14	+
	+	25	5	42	18	+
	+	50	4	-	-	+
Compazine	+	45	4	32	24	+
	+	100	26	45	35	0
	0	200	56	53	33	0
	+	40	3	53	24	0
Phenergan	+	100	23	35	26	+
	+	65	32	49	26	
Serpasil	+	7.5	2	56	30	0
Sparine	+	100	35	39	25	+
Stelazine	+	40	3	49	22	
	+	25	2	54	30	+
	+	90	12	38	28	+
	+	33	1	46	20	+
	+	100	27	39	33	+
	+	25	2	39	33	+
	+	50	3	42	24	+
	+	30	2	38	31	
Thorazine	+	85	23	42	28	0
	+	100	31	47	27	0
Trilafon	0	100	5	38	31	
	+	65	47	31	29	0
	+	90	26	39	26	+
	+	300	45	38	29	0
	+	25	3	58	30	0
Quinidine	+	53	1	42	27	+
	+	28	1	67	34	+
	+	50	2	42	32	0
	+	110	31	47	31	0

*VF = Ventricular fibrillation.
†NSR = Normal sinus rhythm.

from one rhythm to the other. No apparent correlation was noted between the type of conversion and the other measured variables. Control perfusions of saline before and after the experimental drugs did not alter the pattern of fibrillation. Representative electrocardiographic tracings showing these results are portrayed in Fig. 2.

2. *Effects of Drugs on the Heart in Normal Sinus Rhythm.*—

The ataractic drugs and quinidine, under conditions of this experiment, produced bradycardia; and in the example illustrated, Stelazine (50 mg.)

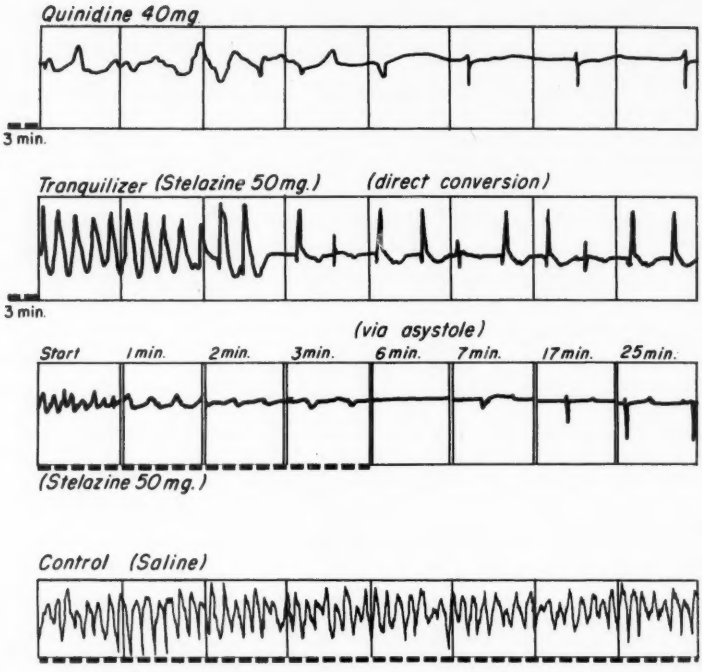

Fig. 2.—Ventricular Fibrillation. Illustrative electrocardiographic tracings are reproduced here to show the direct conversion to a normal sinus rhythm 3 minutes after the administration of quinidine or Stelazine. The third line shows the intermediary state of cardiac asystole. Typical saline control tracing is shown for comparison. Time lines are at 1-second intervals. Paper speed in recorder is 25 mm. per second. The interrupted heavy line denotes time of continuous drug administration.

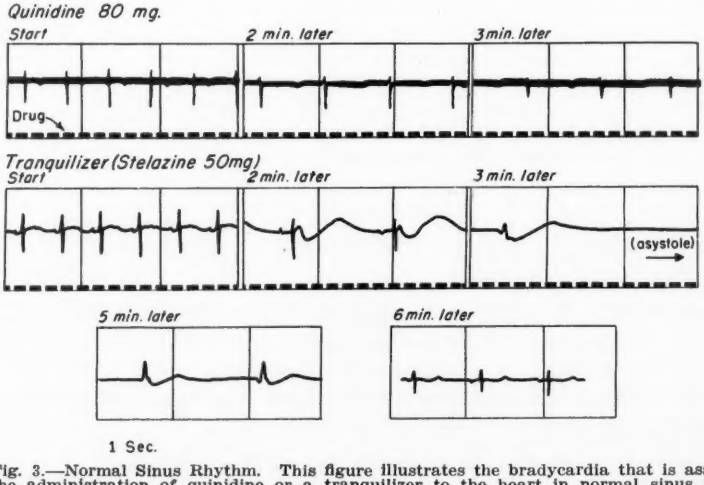

Fig. 3.—Normal Sinus Rhythm. This figure illustrates the bradycardia that is associated with the administration of quinidine or a tranquilizer to the heart in normal sinus rhythm. In the second instance, cardiac asystole resulted with return of normal electrocardiogram after cessation of the drug.

produced asystole at the end of a 3-minute infusion. Subsequent recovery with a normal electrocardiogram is shown after cessation of the drug in Fig. 3.

3. *Subsequent Protection Against the Artificially Induced Ventricular Fibrillation.*—

This was demonstrated in 17 of 26 instances in the tranquilizer groups, and in 2 of 4 trials in the quinidine group. This was not observed in 76 trials in the control group.

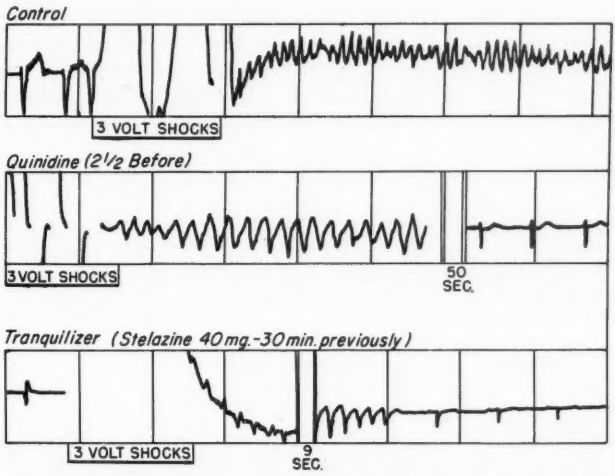

Fig. 4.—Drug-induced protection vs. low-voltage shock ventricular fibrillation. The first line shows the electrocardiographic tracing of a heart in normal sinus rhythm subjected to 3 volt shocks and the resulting pattern of ventricular fibrillation. Spontaneous reversal to normal sinus rhythm does not occur in several hours of follow-up.

The center tracing shows the residual protective effect of quinidine with "spontaneous" reversal to a normal rhythm within a minute of the low-voltage shocks.

The third tracing shows a similar protection afforded by Stelazine, which had been given 30 minutes prior to the administration of the low-voltage shock. Note the rapid return to a normal sinus rhythm.

TABLE II. SUBSEQUENT PROTECTION AGAINST VENTRICULAR FIBRILLATION

	TRIALS	APPARENT PROTECTION	NO APPARENT PROTECTION
Saline	76	0	76
Ataractic drugs	26	17	9
Quinidine	4	2	2

The duration of this protection was variable but, on the average, lasted about 30 to 45 minutes. These results are included in the last column of Table I. Illustrations of representative electrocardiographic tracings are reproduced in Fig. 4.

DISCUSSION

As indicated in earlier remarks, this represents a preliminary report of exploratory work currently in progress. There is much more to assess before the possible application of this information is indicated. Nevertheless, with the

widespread use of the ataractic or tranquilizer drugs, and with the apparent low incidence of side effects or complications, the possible clinical usefulness of these agents in preparing a patient for cardiac surgery immediately becomes apparent. A case in point is that of V. B. L., aged 10, a patient with a large ventricular septal defect and pulmonary hypertension (PA pressure 90/40). On each physical examination in the period of preoperative evaluation, the rhythm of his heart was characterized by frequent premature ventricular contractions. Because this had been noted without exception by several examiners over a period of 3 months, and a tracing again confirmed frequent ventricular extrasystoles, he was given a small dose of an oral tranquilizer and a repeat electrocardiogram was taken 24 hours after the previous one. No irregularities were observed on the oscilloscope in 1 hour of observation. The electrocardiograms are reproduced in Fig. 5. This patient subsequently underwent open heart

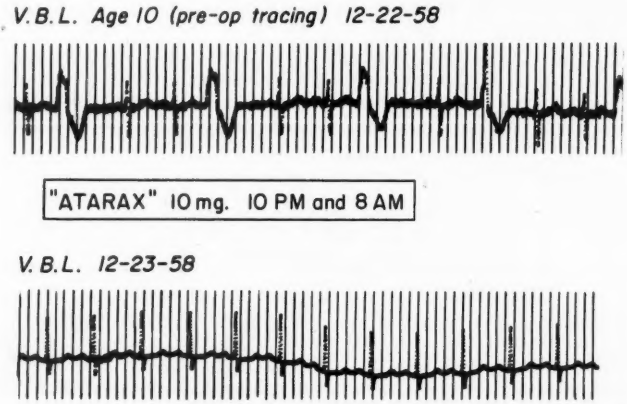

Fig. 5.—Ventricular Septal Defect With Pulmonary Hypertension. Note the disappearance of the frequent premature ventricular contractions after small doses of a tranquilizer agent.

surgery for repair of the ventricular septal defect and has made an uneventful recovery. Other clinical experience is similarly suggestive of beneficial effects, but lack of precise controls makes interpretation and evaluation difficult.

It is interesting to postulate that the hypotension which occasionally follows the use of these drugs may, in some cases, be due to a direct cardiac effect.

CONCLUSIONS

1. Under conditions of these experiments, employing the biologically supported isolated canine heart preparation, infusion of an ataractic drug into the coronary circulation is capable of converting ventricular fibrillation into a normal sinus rhythm.

2. In the majority of instances, residual protection follows the administration of an ataractic drug against the artificial production of ventricular fibrillation by repeated low-voltage shocks.

3. These drugs are quite similar to quinidine in the direct effect on the rhythm of the canine heart.

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(For Discussion, see page 638.)

THE MECHANISM OF VENTRICULAR FIBRILLATION AND CARDIAC ARREST DURING SURGERY

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INTRODUCTION

THE BEST approach to the problem of ventricular fibrillation and cardiac arrest is prevention. This implies an understanding of the mechanisms underlying their production. Many factors have been incriminated as the basis for these phenomena. However, their proof requires a technique for producing ventricular fibrillation and cardiac arrest under controlled experimental conditions in which each factor or combinations of factors can be evaluated.

In studies of the phenomena attending drowning in various species we have noted, as have others, that some animals succumb to ventricular fibrillation, whereas others die from cardiac arrest. Careful tests indicate that the former results from extreme ionic imbalances due primarily to rapid and explosive shifts in potassium. The cardiac arrests are almost exclusively the result of anoxia without serious ionic imbalances.[1]

It would appear that factors producing anoxia and ionic shifts might well be responsible for the occurrence of ventricular fibrillation and cardiac arrest during surgery. This study was undertaken to investigate this premise.

EXPERIMENTAL DESIGN

It is known that rapid injections of various ions can produce ventricular fibrillation.[2] We have seen this result from potassium, calcium, and magnesium, and are assured that it may happen with other substances. However, in human and animal systems, the only ion which can be mobilized from its depots and translocated through the body rapidly enough and in large enough amounts to produce sudden severe cardiac arrhythmias and ventricular fibrillation is potassium.[3, 4]

Therefore, we have used potassium chloride in graded doses to induce cardiac arrest and ventricular fibrillation and study the time-dose relationship.

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This has allowed us to determine the serum potassium level which must be reached within a certain time in order to produce these phenomena.

Having established the fibrillating and arrest doses of potassium, we have then investigated the ionic changes which result from various factors operating singly or in combination during surgical procedures. These include: anoxia, stress, hemorrhage, hypercarbia, and drugs.

METHODS

Healthy, normal dogs under Nembutal anesthesia have been used for the studies. Following intubation with a cuffed endotracheal tube, all animals have been heparinized with 1 mg. per kilogram to prevent clotting during collection of multiple blood specimens. Femoral artery pressure was measured directly on a Sanborn Twin-Viso Recorder by means of a pressure transducer. Lead II electrocardiograms were monitored continuously during most of the procedures. Potassium chloride solution was prepared with a concentration of 100 mg. per cubic centimeter and diluted with sterile water to the proper volume for injection. All KCl and drugs were injected very rapidly through a No. 16 catheter in the opposite femoral vein. Blood samples were withdrawn with a large caliber needle from the carotid artery, or were bled off directly from this source.

RESULTS IN THE VARIOUS SERIES

Effect of Potassium Injection.—

Sixty dogs were injected witih varying amounts of potassium chloride. These injections were given very rapidly, usually within 2 to 4 seconds. Blood specimens were taken every *10 seconds* for determination of serum potassium levels.

Fig. 1, *B,* summarizes the results of this work. Ninety per cent of the animals which received 20 mg./Kg. went into ventricular fibrillation. One dog did not show fibrillation. This amount apparently represents the "fibrillating dose" of potassium. Less than this causes either no fibrillation (10 mg./Kg.) or only a small incidence (15 mg./Kg.). At the 50 and 60 mg./Kg. level, 40 to 60 per cent of the animals showed ventricular fibrillation, and the rest went into cardiac arrest. Cardiac arrest resulted at the 70 mg./Kg. level, without ventricular fibrillation in every case.

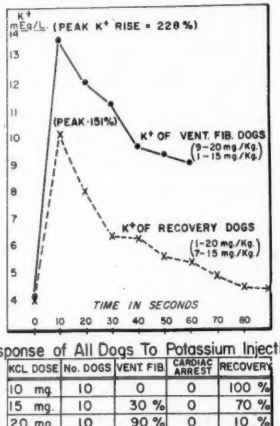
Fig. 1, *A,* shows the mean serum potassium response of all dogs which received 15 mg./Kg. and 20 mg./Kg. All animals which had a potassium rise of 200 per cent or more above their base level within 10 seconds following injection went into ventricular fibrillation. Dogs with peak potassium values of less than 200 per cent within 10 seconds recovered and did not fibrillate.

Fig. 2 presents the data on the 15 mg./Kg. and 20 mg./Kg. series. These data substantiate the time-dose relationship between potassium and ventricular fibrillation. Here, again, the first injections which resulted in elevation of serum potassium level to 200 per cent or more above the base level caused ventricular fibrillation. The animals which did not fibrillate received a second

injection of the same amount 30 minutes later. All animals with potassium elevations of 200 per cent, resulting from the second injection, experienced ventricular fibrillation.

Potassium Injection Series

A. Mean Serum K^+ Response in All Dogs Receiving 15 mg. KCl/Kg. and 20 mg. KCl/Kg.


K+ mEq/L
(PEAK K+ RISE = 228%)
(PEAK-151%)
K+ OF VENT. FIB. DOGS (9-20 mg./Kg. 1-15 mg./Kg.)
K+ OF RECOVERY DOGS (1-20 mg./Kg. 7-15 mg./Kg.)
TIME IN SECONDS
0 10 20 30 40 50 60 70 80

B. Response of All Dogs To Potassium Injection

KCL DOSE	No. DOGS	VENT FIB.	CARDIAC ARREST	RECOVERY
10 mg.	10	0	0	100 %
15 mg.	10	30 %	0	70 %
20 mg.	10	90 %	0	10 %
40 mg.	4	100 %	0	0
50 mg.	13	60 %	40 %	0
60 mg.	9	45 %	55 %	0
70 mg.	5	0	100 %	0

Fig. 1.

Potassium Injection Series

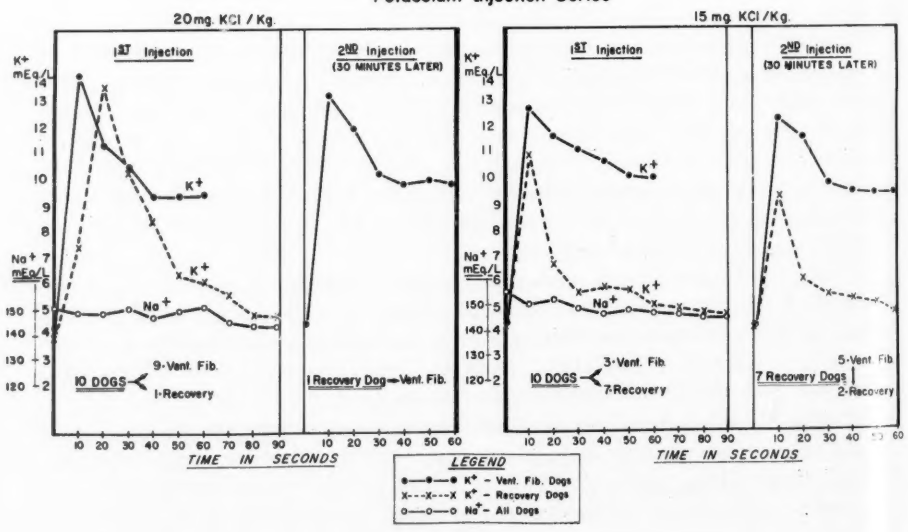


Fig. 2.

Fig. 2 reveals an interesting observation in the 20 mg./Kg. series. When the potassium peak was 200 per cent but was reached in 20 seconds instead of 10 seconds, ventricular fibrillation did not result. The time-dose-response relationship here is such that a specific dose must be injected within a specific time and result in a specific potassium rise within a specific period. These studies indicate that to produce vetricular fibrillation, 15 mg./Kg. must be injected intravenously within 2 to 4 seconds and cause a 200 per cent elevation in serum potassium level above the base line within 10 seconds following injection. The animal cited in the 20 mg./Kg. series probably did not fibrillate because the injection took longer than 4 seconds. We have noted several times that doses of KCl, which usually produced fibrillation when injected within 4 seconds, failed to do so when the injection took 5 or more seconds. Another observation to substantiate this is that amounts of potassium as large as 300 mg./Kg. injected over a period of 1 minute did not cause ventricular fibrillation or cardiac arrest.

In those dogs in which large doses of potassium produced arrest, the peak serum level showed a rise of between 600 and 1,000 per cent. All of the 70 mg./Kg. animals showed such responses. However, in the 50 mg./Kg. and 60 mg./Kg. series no specific relationship could be found between per cent elevation of serum potassium and incidence of ventricular fibrillation or cardiac arrest.

Serum sodium levels showed no significant change in these animals.

Effect of Anoxia.—

Having established the serum potassium level and timing required to produce ventricular fibrillation, we next evaluated various factors which might be operative during surgery and which could reproduce these phenomena under clinically simulated conditions. These factors included anoxia,[5, 6] stress,[7, 8] hemorrhage,[3, 4] hypercarbia,[9-12] and drugs.[13]

Acute anoxia was produced in 9 dogs by tracheal clamping. They showed a mean potassium rise of 51 per cent within 5 minute. Ventricular fibrillation did not occur. They all progressed to bradycardia and ultimately to cardiac arrest. These results are summarized in Fig. 3.

Chronic anoxia was studied in 7 dogs which rebreathed into a bag through a soda lime cannister to prevent carbon dioxide accumulation. Within 10 minutes their mean potassium level had risen to 53 per cent. One animal went into cardiac arrest at 8 minutes with a 16 per cent potassium rise. The others experienced bradycardia and cardiac arrest. One animal went from cardiac arrest into ventricular fibrillation after 12 minutes of anoxia. This ventricular fibrillation represents a terminal cardiovascular phenomenon common to dying hearts rather than the cause of death.

These results indicate that "pure" anoxia results in cardiac arrest and is seldom, if ever, a cause of ventricular fibrillation.

Effect of Epinephrine.—

To simulate severe stress, intravenous epinephrine was administered to 72 dogs. The first 11 animals were injected with 0.05 mg./Kg. The serum potassium level began to rise significantly at 30 seconds and reached a peak of 88

per cent above the base level within 1 minute. No dog experienced ventricular fibrillation; the serum potassium level returned to normal in 4 to 5 minutes and all dogs recovered.

To determine if this was a maximum response, twice as much epinephrine (0.10 mg./Kg.) was administered to another series of 11 dogs. These animals showed exactly the same response. Epinephrine produced no change in the serum sodium level in any of these animals. These results are detailed in Fig. 3

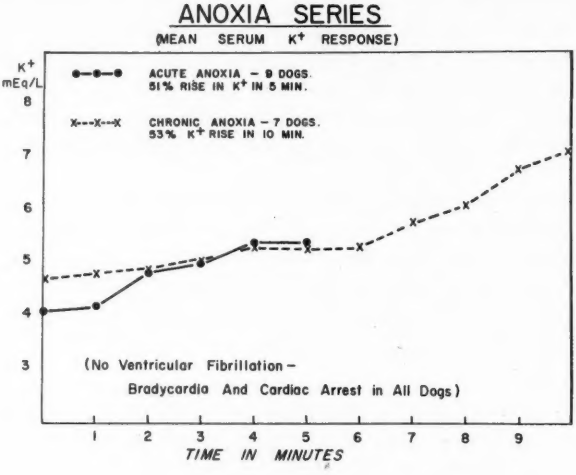


Fig. 3A.

TABLE I. INTRAVENOUS EPINEPHRINE SERIES

ADMINISTRATION	NUMBER DOGS	PEAK K+ RISE IN PER CENT*	
		0.05 MG./KG.	0.10 MG./KG.
A. *Single Dose Series*	11	88	
	11		93
B. *Summation Series* (Two doses each)			
1. 15 seconds apart	6	90	
2. 30 seconds apart	4	84	
3. 60 seconds apart	4	105	
C. *Repeat Dose Series* (Two doses each)			
1. 10 minutes apart	12		
1st dose		84	86
2nd dose		80	78
2. 20 minutes apart	12		
1st dose		82	84
2nd dose		73	80
3. 30 minutes apart	12		
1st dose		89	84
2nd dose		83	80

*In all series (1) the serum potassium rise started within 30 seconds following the injection, (2) the peak potassium level was attained in 60 to 90 seconds after injection, except B-2 (105 seconds) and B-3 (120 seconds), and (3) the serum potassium level returned to the initial level within 4 to 5 minutes, except B-2 (6 minutes) and B-3 (8 minutes).

To determine whether a series of stresses in close succession might produce a cumulative response with respect to potassium elevation, a series of dogs received two injections of 0.05 mg./Kg. each, separated by intervals of 15, 30, or 60 seconds. The results recorded in Table I indicate that these dogs had essentially the same response as the animals which received only a single injection.

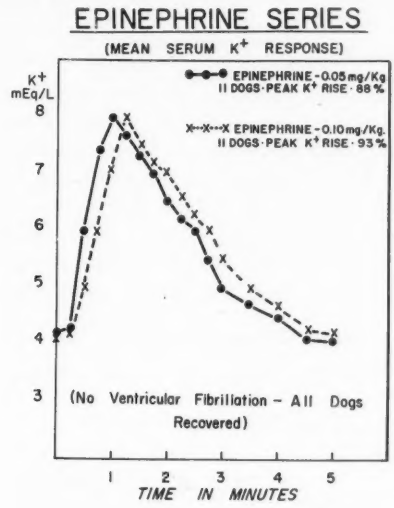

EPINEPHRINE SERIES
(MEAN SERUM K+ RESPONSE)
K+ mEq/L
EPINEPHRINE - 0.05 mg/Kg
11 DOGS · PEAK K+ RISE · 88%
X--X--X EPINEPHRINE - 0.10 mg/Kg.
11 DOGS · PEAK K+ RISE · 93%
(No Ventricular Fibrillation - All Dogs Recovered)
TIME IN MINUTES

Fig. 3*B*.

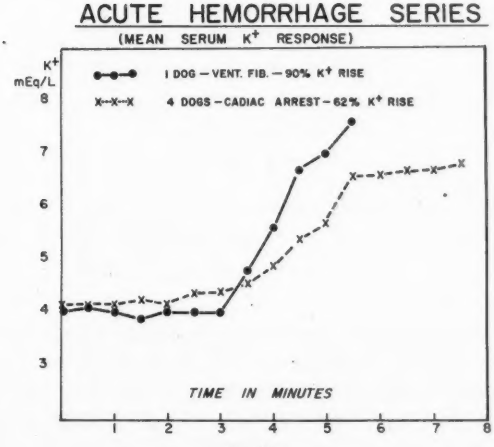


Fig. 3*C*.

To determine the effect of stress produced at intervals of 10, 20, or 30 minutes, 12 dogs in each of 3 series received two doses of either 0.05 mg./Kg. or 0.10 mg./Kg. at these time intervals. As indicated in Table I, all animals

showed the same peak potassium rise as the animals which received a single injection. The only consistent difference was that the second dose always elicited a slightly diminished rise in potassium.

In all animals, the serum potassium rise started within 30 seconds following the injection; the peak potassium level was usually attained in 60 to 90 seconds after injection, and the serum potassium level returned to normal values within 4 to 5 minutes.

Severe stress (epinephrine) alone did not result in ventricular fibrillation in any animal.

Effect of Hemorrhage.—

Another important factor which may cause elevation of serum potassium during surgery is acute hemorrhage. This was evaluated in 5 dogs by withdrawing 50 c.c. of blood every 30 seconds. After 3 minutes, these animals showed a significant rise in serum potassium level. One animal fibrillated at 5 minutes with a serum potassium rise of 62 per cent. The other 4 animals showed a serum potassium plateau at about this same level and then rose to a peak

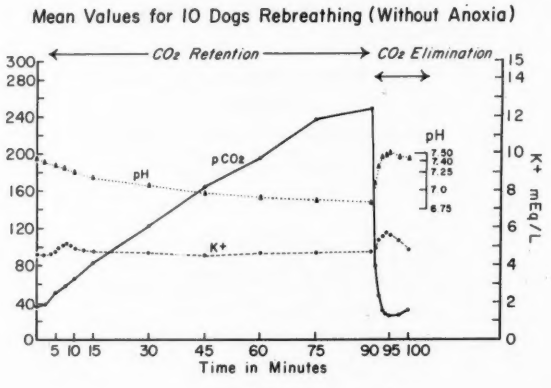


Fig. 4.

potassium of 90 per cent above normal between 7 and 8 minutes, when they expired from cardiac arrest due to exsanguination. Fig. 3 summarizes these findings.

Effect of Hypercarbia.—

Hypercarbia, independent of anoxia, was investigated by having 10 dogs rebreathe continuously for 90 minutes into a large rubber bag. Anoxia was prevented by replacing the oxygen as utilized. At the end of this time the bag was removed and the animals were subjected to hyperventilation with room air for 1 minute and then allowed to breathe spontaneously. After an initial transient rise the serum potassium level remained constant throughout the period of CO_2 retention. The pCO_2 climbed from 40 to 240 during this time. At the time of rapid CO_2 elimination, the pCO_2 dropped precipitously to subnormal levels during 2 to 3 minutes. Simultaneously the potassium level rose 24 per cent above the base level. Cardiac arrhythmias occurred in every dog

at the time of CO_2 reversal. Nine of the dogs recovered but one progressed from ventricular tachycardia into ventricular fibrillation 4 minutes after the hyperventilation. Fig. 4 illustrates these results.

Effect of Drugs.—

Numerous anesthetic agents and drugs are known to have sensitizing, excitatory, depressant, and other effects on the heart. It was not within the scope of this paper to investigate these thoroughly. However, a well-known combination was used to demonstrate drug effect on serum levels. After preliminary sedation with Nembutal, 7 dogs were anesthetized with chloroform. When they were in stage III anesthesia, specimens of blood were drawn during a fifteen-minute control period for determination of serum levels of calcium, sodium, potassium, magnesium, and chloride.

Then a rapid intravenous injection of 0.05 mg./Kg. of epinephrine was made. Blood was drawn every 15 seconds thereafter for 2 minutes and then every ½ minute for 3 additional minutes. The findings are summarized in

Ionic Response to Epinephrine During Chloroform Anesthesia.

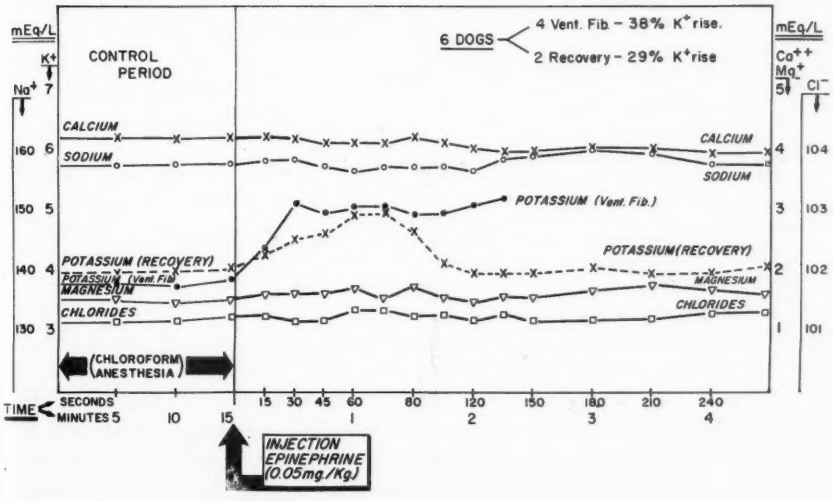


Fig. 5.

Fig. 5. None of the ions showed any significant change except the potassium. Four of the dogs went into ventricular fibrillation with a serum potassium rise of 36 per cent. Two others had a peak potassium level of 25 per cent and recovered without fibrillating. One of the dogs received an overdosage of the anesthetic agent prior to the administration of epinephrine and died an anoxic death with cardiac arrest from the myocardial depression, as would be expected.

Effect of Summation of Factors.—

In the previous studies, great care was taken to evaluate the effects of single uncomplicated factors and situations. Such pure situations may occur

clinically, but they are not the rule. They are essential in establishing base-level effects, but should be supplemented by studies of combinations of factors as might be anticipated on a practical basis. Accordingly, the effects of anoxia in combination with other factors were studied. The results in 65 dogs are summarized in Table II.

TABLE II. SYNERGISM OF FACTORS SERIES

FACTORS	NO. DOGS	RESPONSE			
		VENTRICULAR FIBRILLATION		CARDIAC ARREST	
		INCIDENCE (%)	PEAK K^+ RISE (%)	INCIDENCE (%)	PEAK K^+ RISE (%)
A. Acute anoxia (4 min.) plus I.V. KCl					
(1) 10 mg./Kg.	12	50	239	25	187
(2) 15 mg./Kg.	12	50	278	42	198
B. Chronic anoxia plus CO_2 retention	9	0	—	100	85
C. Acute anoxia plus simultaneous epinephrine*	4	50	120	50	80
D. Chronic anoxia plus CO_2 retention plus epinephrine*	4	25	50	75	116
E. Epinephrine* 30 sec. before acute anoxia	4	50	89	50	81
F. Epinephrine* 60 sec. before acute anoxia	4	75	86	25	86
G. Epinephrine* 120 sec. before acute anoxia	4	50	100	50	88
H. Epinephrine* 30 sec. after acute anoxia	4	25	84	75	135
I. Epinephrine* 60 sec. after acute anoxia	4	25	106	75	93
J. Epinephrine* 120 sec. after acute anoxia	4	50	92	50	81

*Epinephrine (0.05 mg./Kg.), when used.

In two series of 12 dogs each, after 3 minutes of acute anoxia, 10 mg./Kg. or 15 mg./Kg. of potassium chloride was administered intravenously and the anoxia was prolonged to 4 minutes (Table II, *A*). In each of these groups, 50 per cent of the animals fibrillated. Twenty-five and 42 per cent of the rest went into cardiac arrest and the remainder recovered. In the 10 mg./Kg. series this represents a 50 per cent increase in ventricular fibrillation and a 75 per cent increase in mortality. In the 15 mg./Kg. group this represents a 20 per cent increase in ventricular fibrillation and a 60 per cent increase in mortality. Furthermore, the peak serum potassium levels in both fibrillating and nonfibrillating animals are higher than those produced by the drug alone. This indicates the potentiality for summation of responses when multiple factors are operating.

A series of dogs with anoxia plus hypercarbia and/or stress (Table II, *B-J*) provided two important observations: (1) in every instance (except chronic anoxia plus CO_2 retention) factors which did not produce ventricular

fibrillation when operating singly, resulted in a 25 to 75 per cent incidence of fibrillation when they operated in combination, and (2) in every instance in which ventricular fibrillation occurred, the peak potassium level was only one half or less than the 200 per cent rise required to produce ventricular fibrillation with potassium chloride injections alone. This indicates that ventricular fibrillation can occur even without summation sufficient to raise the potassium to fibrillating levels. Apparently this is due to the synergistic effects of the factors. An attempt to determine the most effective synergistic sequence was not too conclusive, but a slightly greater fibrillatory effect from stress preceding anoxia was indicated.

Hypercarbia and chronic anoxia are both depressant. Although this combination elevated the serum potassium level, cardiac arrest occurred without ventricular fibrillation. In all other instances in which ventricular fibrillation did not occur, the anoxia was maintained until cardiac arrest occurred.

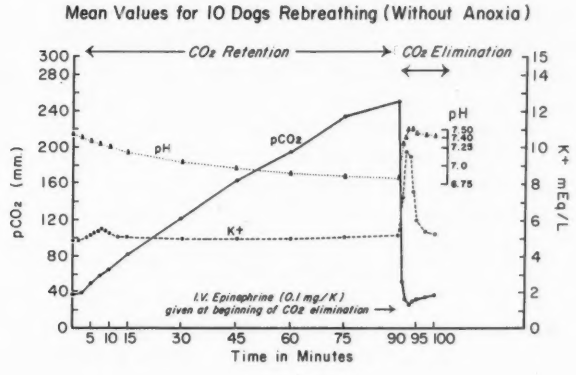


Fig. 6.

Fig. 6 presents the summation resulting from rapid reversal of severe hypercarbia simultaneously with stress (I.V. epinephrine). This combination of factors resulted in an 88 per cent rise in serum potassium.

The electrocardiograms showed more severe changes in this second group than in the preceding group of rapid reversal of hypercarbia. Nine of the 10 dogs developed ventricular tachycardia, 1 of which progressed into ventricular fibrillation. This animal had a 171 per cent rise in serum potassium.

COMMENTS AND SUMMARY

Two hundred and forty-six dogs have been studied in this survey of the mechanisms underlying ventricular fibrillation and cardiac arrest during surgery. Results indicate that cardiac arrest is primarily a manifestation of anoxia and the most ominous sign of impending disaster is bradycardia. On the other hand, ventricular fibrillation results from profound and sudden ionic imbalances. Experimentally such imbalances can be produced by a variety of substances, but clinically only potassium is capable of being mobilized with the

speed and amplitude required to produce this lethal complication. Various factors, such as anoxia, hypercarbia, hemorrhage, stress, drugs, and anesthetic agents, are capable, independently and in combination, of causing significant elevations in serum potassium. These elevations are precipitous and profound. Accurate appraisal requires monitoring them on a second-to-second basis.

Careful studies by Houssay and collaborators[3, 4] have revealed that the source of these potassium discharges is the liver. As a result of such noxious stimuli as anoxia, stress, reflex responses, hemorrhage, excitation, among others, the sympathetic nervous system and/or the adrenals act through nervous pathways to liberate the potassium-hexose-phosphate complex from the liver. Usually this is an efficient defense system of the body since the glucose provides energy and the potassium augments myoneural discharge in these emergencies.

However, if these act very rapidly, they result in a sudden shift of potassium into the blood stream and directly to the heart. The sudden appearance of large concentrations of potassium in the extracellular compartment results in large differences in electrical potential across the myocardial cell membrane. At low concentrations, little effect occurs except on the rate and rhythm of the heart. At higher concentrations (i.e., 20 mg./Kg.) local areas are triggered by differences in potential and ventricular fibrillation results. At very high concentrations, it appears that the myocardium is suddenly depolarized and overwhelmed into arrest by the massive transfer of ions.

The serum potassium level rapidly returns to normal levels because this ion is quickly translocated into muscle and body tissues. It is then gradually transferred back to its storehouse in the liver.

It has been shown here that various factors stimulating the release of potassium can act simultaneously or in sequence to produce summation. Of even greater significance is the fact that some of these factors and drugs and anesthetic agents act to sensitize, stimulate, irritate, or depress the myocardium. This provides further synergism.

An evaluation of the use of drugs or other ions to prevent or counteract the effects of anoxia and/or ionic imbalances is outside the realm of this paper. Preliminary studies on a series of 10 dogs have indicated that atropine is only slightly protective against the fibrillatory effect of 20 mg./Kg. of potassium chloride. In another series of 10 dogs, acetylcholine appeared to be somewhat more protective against the effects of 15 and 20 mg./Kg. of KCl.

However, this approach to the problem begs the basic issue regarding the cause of ventricular fibrillation and cardiac arrest during surgery. If anoxia, stress, hemorrhage, hypercarbia, and drug stimulation and depression underly the mechanism for these complications, the elimination or control of these factors provide the best means of preventing ventricular fibrillation and cardiac arrest.

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(For Discussion, see page 638.)

PREVENTION OF POSTHYPERCAPNEIC VENTRICULAR FIBRILLATION IN DOGS

Bernard Goott, M.D. (by invitation), and Fletcher A. Miller, M.D. (by invitation), Minneapolis, Minn.

VENTRICULAR fibrillation can be consistently produced in dogs, if, following prolonged hypercapnia, their arterial blood pH is rapidly raised to normal by ventilation with room air.[1] This procedure offers a consistent and reproducible method of studying the metabolic alterations which might be of influence in the production of ventricular fibrillation.

Inhalation of high concentrations of carbon dioxide results in a rise in the levels of potassium, inorganic phosphorus and glucose, with a simultaneous drop in the ionized calcium level. The ratio of ionized calcium to potassium shows a further decrease in the immediate posthypercapneic period when concurrent with the return to more nearly normal blood pH levels there is a sudden elevation of the serum potassium and a simultaneous drop in the ionized calcium.[2] In all likelihood, these values are indicative of an acute ionic alteration in the myocardium.

According to Tenney,[3] carbon dioxide inhalation serves as a potent stimulus to the sympatho-adrenal system. The circulatory changes and the metabolic alterations of hyperkalemia, hyperphospheremia, and hyperglycemia described above are all consistent with increased sympatho-adrenal activity.

In order to explore the possibility that these metabolic changes may be important in the precipitation of this type of fibrillation, the following investigations were undertaken.

A. *Sympatho-Adrenal Influence.*—To examine the influence of the cardiac sympathetic nerves an attempt was made to denervate the heart by means of bilateral sympathectomy. In a second series, Dibenzyline was given in an attempt to suppress the sympatho-adrenal response.

B. *Ionic Balance.*—The significance of the changes in ion concentrations was investigated as follows: (1) calcium gluconate was administered to a series of 12 dogs while inhaling the carbon dioxide mixture, and also in the immediate

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posthypercapneic period, (2) a second series of animals received magnesium sulfate, and (3) in another series, we attempted to suppress the rise in serum potassium by the use of insulin or corticoid preparations.

C. *The Effect of Quinidine Was Also Examined.*

METHODS

Healthy mongrel dogs weighing between 16 and 20 kilograms were used. Each animal was lightly anesthetized with sodium Pentothal, 10 mg./Kg., in order to perform the minor surgical procedures of femoral artery cannulation and tracheotomy. On recovery of the major reflexes, a mixture of 30 per cent

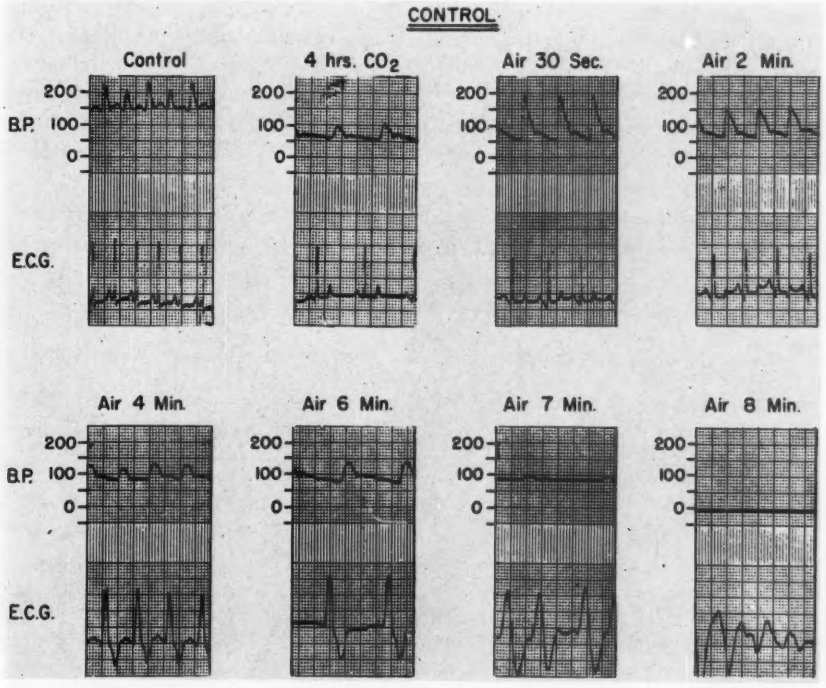

Fig. 1.—Lead II electrocardiographic and blood pressure tracings in a control experiment.

CO_2/70 per cent O_2 was administered via the tracheotomy for a period of 2 hours, followed by a mixture of 40 per cent CO_2/60 per cent O_2 for a second 2-hour period. The dogs were next rapidly hyperventilated with room air using a mechanical respirator with an inspiratory pressure of 20 mm. Hg.

Samples of arterial blood were taken at regular intervals for chemical analysis, and continous electrocardiographic and arterial blood pressure tracings were obtained.

RESULTS

Controls.—A control experiment was performed, in the manner described above, at intervals throughout the series. Of 15 dogs so tested, 14 developed ventricular fibrillation within 10 minutes after being returned to room air inhalation. Fig. 1 illustrates these results.

Thoracic Sympathectomy.—In 10 dogs, bilateral thoracic sympathectomy and cervical ganglionectomy were performed; via bilateral thoracotomy in 9 dogs. In the remaining animal a sternal splitting procedure was employed. The animals were given a recovery period of 2 weeks before subjecting them to the hypercapnia procedure. Only the animal with the sternal split-type incision exhibited fibrillation; none of the others even demonstrated arrhythmias.

A control study for the sympathectomy series was performed by subjecting 5 dogs to bilateral thoractomy without denervation. None fibrillated. Our only explanation for these results is that lateral thoracotomy interferes, probably because of adhesions, with the adequate respiratory exchange necessary for this procedure. The fact that the only dog to fibrillate had had a sternal split-type incision, a procedure resulting in only a minimal disturbance of pulmonary mobility, lends support to this thesis.

An experiment to test the posthypercapneic effect on the same day as the sympathectomy was performed. These animals were intolerant to the carbon dioxide exposure and most of them fibrillated during the hypercapneic period. Table I presents the results of the sympathectomy experiments.

TABLE I. EVALUATION OF SYMPATHECTOMY UPON POSTHYPERCAPNEIC VENTRICULAR FIBRILLATION

	NO. OF EXPERIMENTS	VENTRICULAR FIBRILLATION
Controls	15	14
Thoracic sympathectomy	10	1
Controls, token thoracotomy	5	0
Procedure immediately after sympathectomy; chest not closed	9	7 (Fibrillation occurred while on CO_2)

The ventricular fibrillation threshold, as measured by Shumway and his co-workers[4] employing an electrical stimulus, was measured in 2 dogs both

TABLE II. FIBRILLATION THRESHOLD BEFORE AND AFTER SYMPATHECTOMY

		DELAY (MSEC.)	MILLIAMP.	pH	TEMP.	BLOOD PRESSURE (MM. Hg)
No. 1						
Control		100	15	7.61	37.5	115/80
Left sympathectomy	(1)	110	13	7.46	37.5	100/75
	(2)	95	15	7.36	37.3	150/80
Right sympathectomy	(1)	100	15	7.5	37.5	115/75
	(2)	95	13			
No. 2						
Control		90	20	7.66	36.5	105/75
Right sympathectomy		95	24	7.57	36.0	80/55
Left sympathectomy		110	20	7.62	36.0	85/60

before and after cardiac sympathectomy.* No alteration in the fibrillation threshold was observed as will be noted in Table II.

Sympathetic Blocking Agents.—Dibenzyline in doses of 2 mg./Kg. was injected intravenously in 7 dogs 15 hours before subjecting them to carbon dioxide inhalation to test the effect of inactivation of the sympatho-adrenal system on the development of ventricular fibrillation. Five of these animals fibrillated and the remaining 2 evidenced marked arrhythmia.

Infusion of Calcium Ions.—Calcium gluconate was administered intravenously to 12 dogs; 2 Gm. were given during the period of hypercapnia and 1 Gm. during the ventilation with air. No dog thus treated fibrillated, and

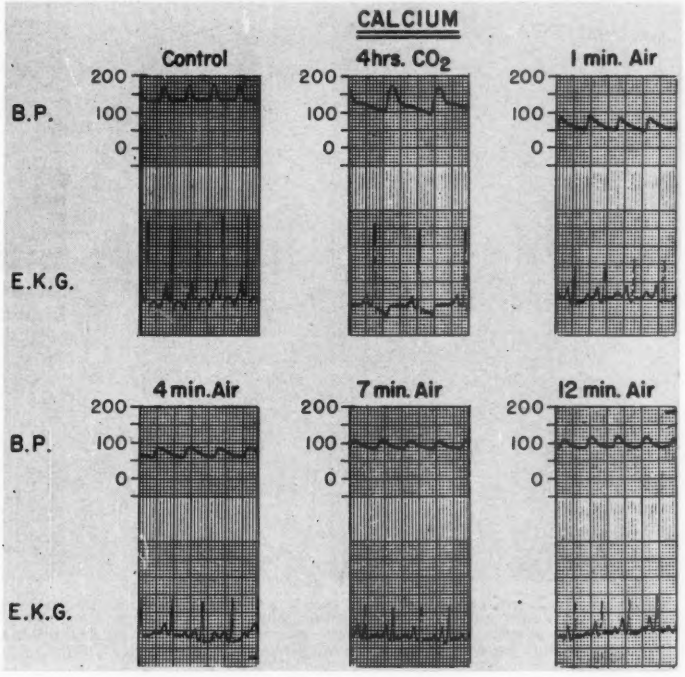

Fig. 2.—Lead II electrocardiographic and blood pressure tracings of a dog treated with intravenous calcium gluconate infusion during acidosis and in the recovery phase. Note the minimal changes in cardiac rhythm. It is possible to revert these arrhythmias by acceleration of the calcium infusion.

arrhythmias in the posthypercapneic period were minimal and even suppressed by accelerating the calcium infusion. These results are illustrated by Fig. 2.

Infusion of Magnesium Ions.—All 6 dogs given intravenous magnesium sulfate in the immediate posthypercapneic period survived the experiment; although in 3 of the dogs marked arrhythmias did occur. This is nicely demonstrated in Fig. 3. The dosage used was 100 to 150 mg./Kg. body weight.

*We are indebted to Dr. Clifford Phibbs for aiding us with these experiments.

Suppression of Serum Potassium Levels.—The work of other investigators has suggested that suppression of the serum potassium rise during the post-hypercapneic state would lessen the incidence of fibrillation.[5, 6]

Because severe respiratory acidosis is associated with hyperglycemia (Table III), we decided to use insulin to suppress this blood sugar rise. Dosage was difficult to estimate and, if excessive, resulted in an extreme drop in blood glucose levels and an inability to tolerate the carbon dioxide inhalation per se. An approximate measure of blood glucose levels was obtained rapidly by the use of blood sugar test paper.

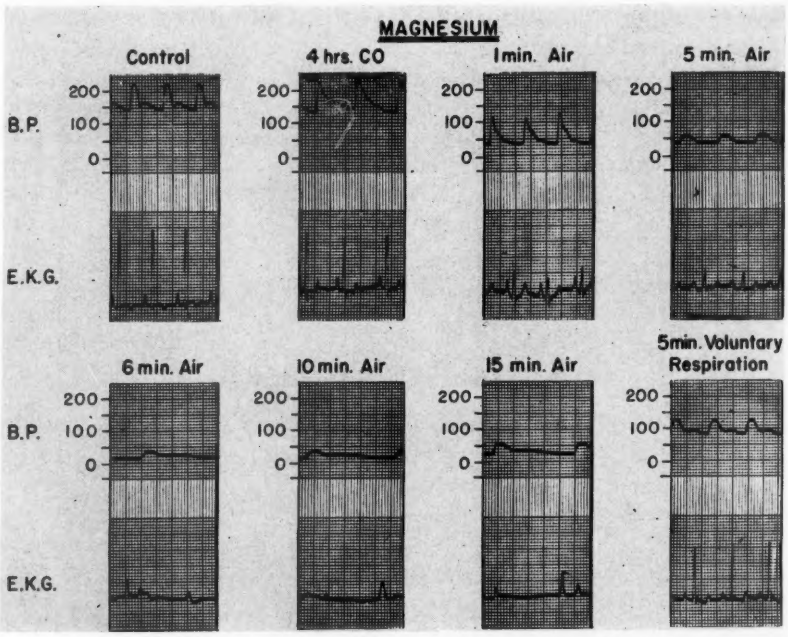

Fig. 3.—Lead II electrocardiograph and blood pressure recording of posthypercapneic dog treated with intravenous infusion of magnesium sulfate. These dogs did develop arrhythmias and other electrocardiographic changes and marked blood pressure depression as illustrated by this tracing, but none of the animals fibrillated.

TABLE III. AVERAGE CHANGES IN LEVELS OF SERUM, POTASSIUM, PHOSPHORUS, AND SUGAR DURING HYPERCAPNIA

	POTASSIUM (MEQ./L.)		PHOSPHORUS (MG. %)		SUGAR (MG. %)	
	CONTROL	4 HR.	CONTROL	4 HR.	CONTROL	4 HR.
Control						
15 dogs	5.2	8.3	4.5	13.9	79	249
Standard deviation	(1)	(2.4)	(1.4)	(2.4)	(11)	(94—Range 134-425)
Dibenzyline						
7 dogs	3.8	7.5	4.6	13.0	76.8	249
Standard deviation	(.06)	(.09)	(1.1)	(3.1)	(148)	(84—Range 176-425)
Corticoid Preparations						
12 dogs	4.5	7.8	4.8	14.3	68.8	250
Standard deviation	(1.9)	(3)	(1.2)	(4.3)	(17)	(42—Range 205-355)

Eight dogs given regular insulin in dosage sufficient to maintain the blood glucose at near control levels tolerated the entire procedure and did not fibrillate. Fig. 4 is typical of the results in the insulin series. The effects on the blood levels of glucose, phosphorus, and potassium can be seen in Table IV. It is evident that the use of insulin prevents the gross elevation of the serum potassium level, but does not reduce the rise in phosphate.

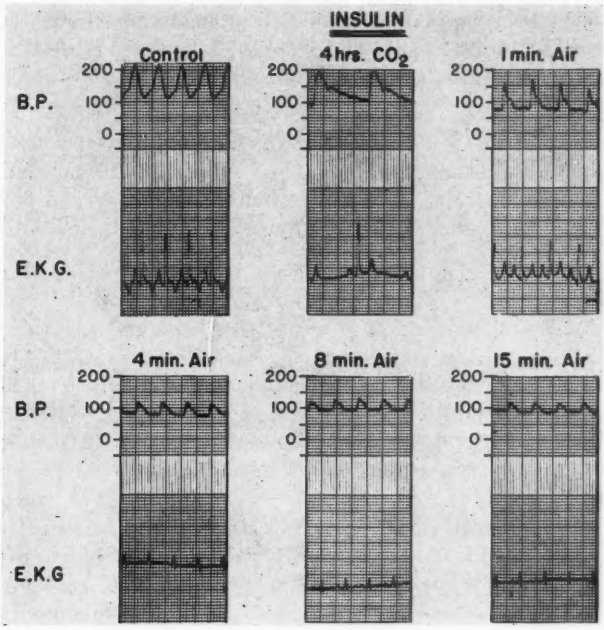

Fig. 4.—Typical Lead II electrocardiographic and blood pressure pattern of a dog treated with insulin during acidosis. Arrhythmias were minimal in all such experiments and blood pressure did not show the typical severe depression.

TABLE IV. EFFECT OF INSULIN UPON THE BLOOD CHEMISTRY DURING HYPERCAPNIA

EXPER. NO.	INSULIN DOSE (UNITS)	POTASSIUM (MEQ./L.)		PHOSPHORUS (MG. %)		GLUCOSE (MG. %)		pH RESULTS*
		CONTROL	4 HR.	CONTROL	4 HR.	CONTROL	4 HR.	
1	10	5.1	6.6					6.69 did not fibrillate
2	10	3.5	4.5	3.3	7.5	85	365	6.73 did not fibrillate
3	20					90	148	6.7 did not fibrillate
4	20	4.5	5.7	5.3	24	100	143	6.65 did not fibrillate
5	25	4.6	4.8	3.2	24	82	30	6.77 did not fibrillate
6	20	3.8	5.4	4.5	24	71	260	— did not fibrillate
7	30	5.1	4.6	3.3	14.5	82	125	6.76 did not fibrillate
8	40	3.8	3.0	4.6	14.5	71	16	6.67 did not fibrillate
Averages		4.3	4.9	4.0	18.1	83	155.3	

*Arterial blood pH obtained just before switch to room air.

Corticoid Preparations.—These drugs are known to lower the levels of serum potassium and inorganic phosphate in normal animals. They were,

therefore, used in an attempt to suppress the levels of these substances during hypercapnia. Two dogs were given an intravenous dose of alphafluorhydrocortone, 1 mg./Kg., 2 hours before the procedure. Fibrillation was not prevented.

Hydrocortone was given intravenously to 10 dogs 2 to 4 hours before the procedure. Dosage varied from 50 to 200 mg. Six of the dogs fibrillated. The results as seen in Table III show that Hydrocortone, in the dosage used, is not significantly beneficial and did not prevent the rise in the levels of serum, potassium, and inorganic phosphorus. It is possible that the effect of these drugs in this regard is inhibited by acidosis.

Quinidine.—Holland[7] has suggested that the antiarrhythmic action of quinidine might be due to depression of the outward flux of potassium across the myocardial cell membrane. Quinidine gluconate, 10 mg./Kg., was administered intravenously to 2 dogs 20 minutes before reversal of the hypercapnia and both fibrillated. Of 6 dogs given quinidine gluconate, 20 mg./Kg., 30 minutes before reversal, 4 fibrillated.

The results of all of these experiments with the changes in blood chemistry are summarized in Tables III, IV, and V.

TABLE V. THE INCIDENCE OF POSTHYPERCAPNEIC VENTRICULAR FIBRILLATION FOLLOWING VARIOUS EXPERIMENTAL PROCEDURES

PROCEDURE	NO. OF EXPERIMENTS	VENTRICULAR FIBRILLATION
Controls	15	14
Calcium gluconate	12	0
Insulin	8	0
Cortisone	12	8
Dibenzyline	7	5
Quinidine	8	6
Magnesium	6	0

DISCUSSION

The maintenance of normal transmembrane potentials in resting cells requires a very definite partition of ions. Calcium and potassium imbalance in particular greatly affect the permeability and excitability of all cardiac tissue and the relative concentration of these ions are as important as the absolute.[8] Whatever the precipitating factors may be, it would seem that sudden changes in ion flux are of extreme importance in the genesis of ventricular fibrillation. Brown and Prasad[2] have shown that in the posthypercapneic dog the ratio of ionized calcium and potassium drops rapidly to nearly one third of normal. Blood samples from the coronary sinus of dogs subjected to hypothermia were found by Covino to show a decrease in ionized calcium and an increase in potassium immediately prior to fibrillation. These changes were not present if the dog did not fibrillate.[9] According to Cherbakoff, when the descending branch of the left coronary artery is ligated to produce fibrillation, there is a marked rise in the level of potassium in the coronary sinus preceding the onset of fibrillation. However, if the rise in

the potassium level is prevented by the administration of insulin and glucose, or bicarbonate, fibrillation is prevented in a high proportion of the animals tested.[10]

The success of calcium, magnesium, and insulin in blocking fibrillation would appear to confirm the importance of an altered myocardial ionic balance in the etiology of fibrillation. Not only did the administration of calcium prevent fibrillation, but severe arrhythmias did not occur. The beneficial effects of magnesium support the contention that this ion has some similarity of action to calcium upon the myocardial cells, especially when the calcium levels are below normal.[8]

The participation of the sympathetic nervous system in response to carbon dioxide stimulation has been adequately demonstrated by Tenney[3] and Fenn.[11] The fact that the metabolic changes of hyperkalemia, hyperphospheremia, and hyperglycemia that occur during the hypercapnia, can also be obtained by Adrenalin administration suggested the use of Dibenzyline to suppress any hyperactivity of the sympatho-adrenal system during carbon dioxide inhalation. However, this sympatholytic agent prevented neither the fibrillation nor the metabolic alterations. Caution must be employed in the interpretation of such results since complete obliteration of this system might not have been obtained by the pharmacologic methods employed.

We believe that the results of our denervation experiments would not substantiate the use of sympathectomy for the prevention of fibrillation. This belief was supported by the failure of sympathectomy to prevent fibrillation as produced by the ligation of the circumflex coronary artery in dogs so tested.

As to the role of the cardiac nerves in the development of ventricular fibrillation, it should be noted that cervical vagotomy had no protective influence on the development of ventricular fibrillation by the experimental method herein employed.

SUMMARY

1. The administration of calcium ions successfully prevented posthypercapneic fibrillation.

2. The administration of magnesium sulfate similarly prevented posthypercapneic fibrillation in all animals so tested.

3. Insulin was successful in preventing fibrillation in all of 8 dogs treated. Administration of insulin suppressed the serum levels of both potassium and glucose during hypercapnia, but did not prevent the rise of the phosphate ion.

4. Corticoid preparations did not suppress the levels of serum potassium and inorganic phosphorus during hypercapnia. Of 12 dogs treated only 4 failed to fibrillate.

5. Quinidine, administered to 8 dogs, failed to prevent fibrillation in 6 of these.

The authors wish to gratefully acknowledge the technical assistance of Mr. Terry Gunther and Earl Levens in performing these experiments.

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DISCUSSION

(PAPERS BY MAGOVERN [PAGE 561], SMITH [PAGE 573], KANTROWITZ [PAGE 586], BRECKLER [PAGE 594], STEPHENSON [PAGE 604], NELSON [PAGE 610], GORDON [PAGE 618], GOOTT [PAGE 630], AND THEIR ASSOCIATES)

DR. HENRY SWAN, II, Denver, Colo.—I would like to make a comment or two regarding the very interesting papers on ventricular fibrillation, which I thought were all extremely productive this morning, and I want to compliment the authors on them.

In regard to the relationship of the central nervous system to fibrillation, I think we should remind ourselves of some interesting work which has gone on in the past, and to ask ourselves how to relate this information to some of the interesting work we heard this morning. I thought Dr. Nelson particularly might like to comment on this.

A year and a half ago, Dr. Montgomery and I, at the Pump-Oxygenator Conference in Chicago, discussed the pharmacology of the heart, and emphasized that the sympathetic innervation to the heart appeared to play an important role in the ability of the heart to undergo ventricular fibrillation when induced by various means.

In 1930, and for a period of several years, Meakin and his co-workers at Wisconsin were studying this problem and the interesting relationship of the actual chemical formula to some of the sympathomedic agents was worked out.

This slide simply shows that the dihydroxy catechol amines, of which adrenalin is a typical example, are fibrillogenic agents, whereas the monohydroxy catechol amines, such as neosynephrine, are not. Thus, there is a definite relationship between the chemical formula and its reaction on the heart.

These workers studied sympathectomy in relation to the stimulus from these dihydroxy catechol amines and they found that if you take out the sympathetic chain down to T-7 you have protected the heart to a large extent from fibrillation induced by catechol amines. But the same effect was also achieved if you left the sympathetic system intact but decerebrated the animal slightly above the midbrain.

Thus, it would appear that the integrity of the sympathetic nervous system to above the level of the midbrain is probably important in the regulation of the ability of that heart to fibrillate.

It is interesting to me that the heart in Dr. Nelson's case was isolated and in this respect I would like to ask him if he feels that this is of any importance in his experiment. On the other hand, Dr. Goott and his co-workers all showed this morning that another stimulus is affected by this sympathetic denervation, namely that of the rapidly changing potassium ion induced by rebreathing after CO_2.

DR. AKE SENNING, Stockholm, Sweden.—First, I wish to take this opportunity to thank you for letting me attend this meeting as a guest. It has really been a fascinating meeting.

Second, I wish to convey warmest regards from my teacher and chief, Clarence Crafoord, especially to the older members of this Association. I do understand his enormous admiration for American thoracic surgery, having visited many of your clinics.

Today I should like to discuss the paper of Stephenson, Edwards, Jolly, and Scott. We have been working with different types of pacemakers outside the patient and inside the patient to treat complete A-V blocks, but we have not been especially happy with any of these types of pacemakers.

The last gadget we have is the one I have in my hand here, as big as a watch, and we have used this experimentally in animals and clinically in 1 case, placing it subcutaneously in the epigastrium. This transistor pacemaker is charged at intervals from the outside by a cord that we place around the patient, and if we wish we can trigger the pacemaker to any desired rhythm with a special induction coil outside.

But we are not pleased with this either, because we have had the same experience as all other people have, that after a while the resistance in the heart, or whatever it is, increases more and more, so that a higher and higher voltage is required, and when one reaches the neighborhood of 20 volts the whole patient jumps, but the heart goes its own rhythm. This takes about 4, 5, or 6 weeks. So I don't think this is the way to tackle this problem. I think we have to seek other ways to treat an A-V block for long periods.

DR. JOHN R. DERRICK, Galveston, Texas.—I would like to discuss the paper of Dr. Nelson in regard to the tranquilizers and their use in preventing cardiac arrythmias.

We have had some experience with a tranquilizer by the name of mepazine, one of the phenothiazines. We used it originally in a group of experiments to prevent fibrillation in cooling animals to cardiac standstill.

[Slide] We premedicated the animals with mepazine, and found that in 45 per cent we could take them down to standstill and successfully resuscitate the animals. One of the disquieting things, however, was that in several instances it required tremendous doses of Adrenalin to resuscitate these animals. In two instances we used as much as 30 and 40 c.c. of 1:1000 Adrenalin.

This demonstrates the cooling process, and you can see the progressive drop in the blood pressures and a progressive slowing of the electrocardiogram down to the point of standstill.

[Slide] In resuscitating the animal, there is a progressive increase in the pulse rate with rewarming and intravenous Adrenalin. We frequently observed a profound hypotension following resuscitation.

We cooled 43 animals by this technique and were able to resuscitate 45 per cent. We have used mepazine clinically in 16 instances, and have found that, in each instance, if it was given as a premedication, the patient seemed to do rather well. We have used it in 5 instances at the time of surgery, and in all 5 the patients developed profound hypotension. The tranquility of the patient was very alarming in these instances.

I would like to compliment Dr. Nelson on his excellent work using a very difficult experimental technique.

DR. DERMONT W. MELICK, Phoenix, Ariz.—My remarks are directed toward the cardiac stimulator, Paper No. 19. I am not quite as pessimistic as our Scandinavian friend.

This is a report of a 50-year-old man with cardiac asystole lasting as long as 30 seconds, complete heart block, and treatment consisted of insertion of a silver wire into the right ventricle and an indifferent electrode in the left axilla. This miniature cardiac pacemaker was obtained through the good offices of Dr. Ehrlich and Dr. Lillehei. This man was on the stimulator for 4 months. At times it was thought it should be stopped, but the patient would not allow it to be stopped. He played golf (without permission); the stimulator stopped by itself at the end of 4 months. At the present time, his rate is 60. He does not have any more periods of syncope.

The only trouble we have had is with the electricians' union, who say we should have a union card for this sort of wiring.

DR. ROBERT S. CARTWRIGHT, Albuquerque, N. M.—We certainly agree with others that tissue hpoxia is the demonstrated principal cause of metabolic acidosis in extracorporeal circulation, and that high flow, normocapnial perfusions using non-acidotic donor blood will usually eliminate metabolic acidosis as a problem. However, we feel it is worth emphasizing that there are other sources of acidosis. Among these is glycolysis, which occurs in extracorporeal blood either before or after perfusion; lacticacidemia which may result from respiratory alkalosis either before or during perfusion; and the possibility of an inadvertent low flow due to arterial cannula obstruction, caval cannula occlusion, or mechanical failure. Acidosis also can occur due to metabolic disease, or renal disease, and is known to exist in patients having cyanotic heart disease. It is common to most major surgical procedures.

Consequently, we feel acidosis should be considered a factor in extracorporeal circulation. Systems in which pH, for example, is used to control the per cent of carbon dioxide in the oxygenator gas mixture will inevitably lead to a hypocapnial perfusion when metabolic acidosis does develop.

Another factor which became evident in our studies was that the use of the Clark electrode in monitoring the venous saturation can lead to inaccurate conclusions since it deals with the vertical portion of the hemoglobin dissociation curve, where pH, pCO_2, and temperature have a marked influence on the relationship between pO_2 and hemoglobin saturation.

DR. HARRISON BLACK, Boston, Mass.—I would also like to discuss the matter of metabolic acidosis occurring during extracorporeal circulation. On the basis of recent experience at Brigham Hospital in Boston, Dr. George Albertal, who has been working with us, introduced a useful change in perfusion technique in an attempt to reduce the degree of this acidosis. Originally we have used 3 per cent CO_2 and 97 per cent O_2 in our Kay-Cross oxygenator. With this mixture normal pCO_2 values in the blood were maintained. However, the pH values fell, the flow was only barely adequate, and the peripheral resistance was elevated. At the end of such perfusions we found an average pH of 7.26 and a bicarbonate level of 17. Two hours later these values had improved only slightly.

In the last 20 cases we have used 100 per cent O_2 in the oxygenator in the hope of compensating for the metabolic acidosis. We have been gratified to find that, while the arterial pCO_2 has dropped into the low 30's, the pH at the end of the run has averaged 7.45. Although the bicarbonate values have still been low (average 16), indicating that there is still some acidosis, the resistance figures have dropped to normal and the patient appears to be able to correct the deficit postoperatively. Thus, 2 hours after the conclusion of such a perfusion the pH has averaged 7.39 and the bicarbonate has risen to 23. The pump flows in these patients have similarly increased from 84 per cent of the preoperative cardiac output when 3 per cent CO_2 was used to 102 per cent with pure oxygen. The suggested beneficial effect on pump flow is being further studied.

DR. J. ANKENEY, Cleveland, Ohio.—I would like to discuss Paper No. 14 and congratulate Dr. Magovern and his associates on a very nice piece of work.

My remarks are very similar to those of Dr. Black. We observed in the laboratory that using 100 per cent oxygen in our Kay-Cross oxygenator, carbon dioxide washout does

not occur, and pH remains more or less constant. Therefore, we elected to omit carbon dioxide in a group of 36 patients and compare the results in this group with 22 patients in which 2 per cent carbon dioxide and 98 per cent oxygen was used.

[Slide] We found that in those cases in which oxygen alone was used, the pCO_2 and pH remained relatively stable throughout the period of perfusion. This was true even if total bypass was carried out over 50 minutes. On the other hand, when 2 per cent carbon dioxide was added to the oxygenator, the pH fell and the pCO_2 rose. We, therefore, concluded that it was not necessary to add carbon dioxide to the oxygenator during total bypass. When carbon dioxide was added, a respiratory acidosis was imposed upon metabolic acidosis which develops to some degree during perfusion.

DR. CONSTANTIN G. CHARONIS, Baltimore, Md.—I want to congratulate Dr. Kantrowitz for his inexpensive pump-oxygenator. I am taking the opportunity to tell you just a few words about the oxygenator that we have developed at the University of Maryland in Baltimore.

Our oxygenator is a disposable disc oxygenator. It has all the advantages of the standard disc oxygenator. It is made of plastic material and comes in packages like intravenous sets, ready to be used. Specialized technicians are not necessary for cleaning and care of the oxygenator. We exhibited our oxygenator last year in Boston, and 2 weeks ago we presented complete data about the oxygenator at the meeting of the Society for Artificial Internal Organs, and will appear in Volume 5 of their transactions.

The entire system, including the disc oxygenator, the tubing, and the bubble filter, costs a little more than $30 plus the cost of sterilization and the shipping.

DR. THOMAS F. NEALON, JR., Philadelphia, Pa.—I would like to say a few words about the very nice presentation of Dr. Smith and his co-workers on the problem of a blood preservative.

He pointed out the need for a better method of preserving blood and also the desirability of a method of converting blood stored in ACD solution to the equivalent of freshly heparinized blood. He also indicated difficulties associated with this.

We have attempted to approach this in a somewhat different manner. [Slide] This has been accomplished by passing the blood over ion exchange resin columns. This slide represents the chemical values in dog's blood before and after storage. Immediately after it was collected and combined with ACD solution, there was a marked drop in the pH, an increase in sodium, and a considerable addition of citrate.

After this blood was stored for 21 days the most important change was the accumulation of potassium and of ammonium. However, in the meantime, because of the increase in lactic and pyruvic acid, as well as phosphates, the pH had dropped further to 6.02. This blood was then passed over two ion exchange resin columns, a cation, and an anion column. Following this, practically all the potassium and citrate were removed, as well as half of the ammonium, phosphate, and lactate. As a result of this, the pH was then brought from 6.02 to 7.0.

This represents just a preliminary study on this work. We have used this blood for exchange transfusions to date in 3 animals. They have tolerated it without any hemorrhagic effects, and within 24 hours all of these chemical studies were normal.

DR. WILFORD B. NEPTUNE, Boston, Mass.—With regard to the problem of donor blood, I would like to mention a technique which we are using with a bubble-type oxygenator which at least has proved successful in our hands. We are no longer using any donor blood whatsoever for priming the pump-oxygenator system nor for support during the perfusion itself. The only blood which the patient receives is ordinary citrated bank blood to replace blood loss from the operative procedure and postoperatively for pleural drainage.

[Slide] This is a selected group of patients to demonstrate various age groups and various body weights, going from 6 to 66 and from a weight of 55 pounds to 159 pounds.

These patients have all been perfused at rates of 65 to 80 c.c. per kilogram per minute. We have done various types of monitoring and physiologic studies and, at least to our interpretation, can demonstrate no adverse disadvantages with this technique.

You can see the types of lesions repaired, and the perfusion times have varied from 15 minutes to a little over 1 hour. In our experience, in perfusions under 30 minutes, we usually use about one or two pints of blood during the procedure and one pint in the next 24 hours to cover pleural drainage. In perfusions from 30 minutes up to an hour or an hour and a half we use three to four pints of blood during surgery and usually one postoperatively.

I call your attention to the 1 patient who received three pints of blood postoperatively. In our total experience, this patient has received the largest single volume of blood during an open heart procedure. The average patient having open heart work on our service receives a total volume of blood which is less than the average patient having a pulmonary resection and, moreover, it is ordinary citrated bank blood and, at least in our experience, we have minimized the problem of procurement, storage, and waste.

DR. THOMAS J. E. O'NEILL, Philadelphia, Pa.—In Paper No. 18, it was stated that there were three principles involved in the currently available heart pumps. I should like to present a fourth type.

This particular principle and invention goes back many centuries ago and was developed first by Archimedes.

[Slide] It differs from the other three principles as the jet airplane engine differs from the old-time piston engine. I am surprised that the aircraft industry didn't think of it first.

Among its advantages is the small size. The largest diameter is less than 8 inches. Its priming volume necessarily is very small. It is quiet in operation and vibrationless. Its output can be regulated carefully from 300 c.c. per minute to 14,000 c.c. per minute.

[Slide] It is easy to clean. It is completely autoclavable, made up of mostly stainless steel and a plastic inner liner, and it can be assembled and dissembled without any tools, just using the fingers, putting together the end plates on slots.

The turbine is a modification of the old water pump of Archimedes, and you can see it here. It rides in the inner lining, which is housed in the outer cylinder. There is a space between these two in which you can circulate fluids to regulate temperatures at any desired level.

Its principal operation: The blood will flow in this direction; rotating on its long axis it effects propulsion, without any valves, by a pulling action, a pushing action, and some centrifugal force. We feel that this is definitely superior to any of the ones presented so far.

A METHOD FOR THE SIMULTANEOUS MEASUREMENT OF MAXIMUM BREATHING CAPACITY, PULMONARY VOLUMINA, AND EFFECTIVE LUNG VENTILATION

George W. Wright, M.D., and Saul R. Gilford (by invitation), Cleveland, Ohio*

IN THE PRACTICE of medicine, information concerning the effectiveness with which the lungs can be ventilated under varying stresses is frequently desired. Measurement of volitional maximal rate of air flow, of distribution of inspired gas, and of the degree to which the lungs can be filled and emptied, will disclose, quantitate, and localize impairments of ventilation, but the time-consuming nature of these measurements has discouraged their widespread application. To minimize this barrier, we have designed and assembled an apparatus to measure simultaneously the maximum breathing capacity (MBC), pulmonary volumina, and a factor reflecting alveolar ventilation. To prepare the apparatus, carry out the test, and make the calculations requires approximately 5 minutes for a single determination.

METHOD

A spirometer inside of which is placed a bag containing 6 L. of oxygen, a meter for continuous analysis of nitrogen, and suitable recording equipment comprises the apparatus. The subject exhales maximally and is then connected to the bag, containing 6 L. of pure oxygen, inside the spirometer. A single full inspiration from the bag records the vital capacity. The MBC is now measured over a 15-second period by rebreathing to and fro in the bag. During this procedure the bag and lung gases come to, or approach, nitrogen equilibrium. At the end of the maximum breathing capacity a maximal exhalation is made into the bag and the subject is turned out of the spirometer. The nitrogen concentration at the mouth is constantly sampled and analyzed and at the termination of the procedure, the nitrogen concentration in the bag is measured by expelling the bag's contents past the sampling point. From these data the residual volume is calculated in the conventional manner for the closed circuit method.[1] No correction for nitrogen excretion or oxygen absorption was made. Knowing the residual volume and the number and volume of

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*Consultant in Instrumentations and Electronics.

each breath, a factor reflecting ventilation effectiveness can be calculated. The tidal volume during nitrogen equilibration can be measured directly or estimated by dividing the total volume respired by the number of breaths taken during the equilibration period.

For purposes of comparison, the MBC was also measured in the conventional manner by volitional maximal hyperventilation for 15 seconds through a face mask and Rudolph (high velocity) valve into a Douglas bag connected by flexible tubing 60 cm. long and 4 cm. in diameter. The conventional open circuit, nitrogen washout method[2] was used for measuring the functional residual capacity and a 13.5 L. Collins spirometer for spirometry. Nitrogen concentration was determined by the Van Slyke apparatus.

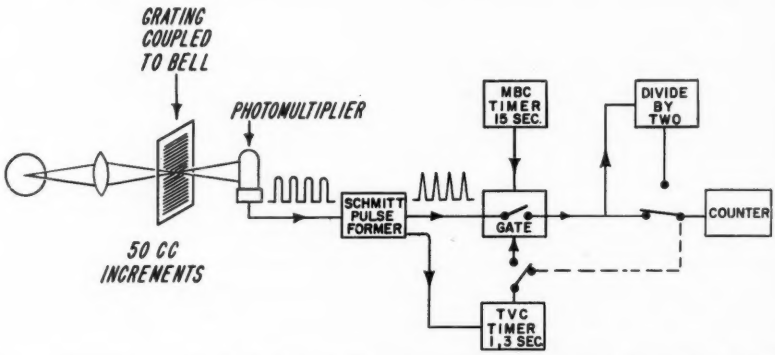

Fig. 1.—Computer channel. Line drawing of signal generator. The light source and grid are contained inside the Krogh type spirometer.

APPARATUS

The spirometer is of the Krogh type, having a bell top measuring 38 × 50 cm., and not counterbalanced. To avoid the inaccuracies imposed by the load and inertial effects of contact writing systems, and to provide a means for immediate display of single (vital capacity) or the sum of multiple (MBC) bell excursions, an optical system was designed for the conversion of bell motion to a measurable signal. In Fig. 1 a block diagram of the instrument is shown.

A light source projects a small spot against a mask having a series of opaque and transparent lines. Each space between the lines represents a volume increment of 50 c.c. and the movement of the mask produces one light pulse for each 50 c.c. deflection. The light pulses are received and amplified by a photomultiplier tube and fed to a Schmitt trigger circuit which generates a sharp electrical pulse for each light pulse. These are fed to the counter circuit through a "gate" system. The "gate" is controlled by a timer circuit permitting pulses to be counted only during the timing interval. For the MBC measurement, a 15-second time interval is used. For timed vital capacity

measurements, a 1- or 3-second interval is selected through a special timer which starts its timing interval only after the first pulse is received. At the same time the counts are passed through a "divide by two circuit" to make the displayed results direct indicating. The counts are fed into a simple computer in the form of a digital counter for adding up the volume increments with proper provision for multiplication of appropriate factors. The results are displayed directly on a counter dial which reads in liters per minute for the MBC measurement, and in fractions of liters for the vital capacity measurements. A second and independent system and circuitry produces an output directly proportional to volume as in a conventional spirometer. This consists of an optical system similar to that of the digital channel but with a mask that is a linearly tapered slot. The amount of light reaching the photocell is a function of the position of the mask and is directly related to the deflection of the bell and therefore to the volume. This channel is used where spirometer patterns are of interest such as recording the tidal volume and changes in mid-position. The output of this channel must be fed into some form of recorder such as an oscilloscope. The spirometer and its signal producing and recording system will be described in technical detail in a subsequent publication.

Continuous sampling of gas was done at the spirometer end of the tubing connecting the face mask with the bag inside the spirometer. The continuous sample was passed through a Water's nitrogen analyzer and recorded on a Texas direct writer. The spirometer channel signaling the tidal volume was also recorded on the Texas direct writer. The response time of the nitrogen meter is less than 0.05 second, and the frequency of the Texas writer is 15 per second.

CRITIQUE OF SPIROMETER AND ITS RECORDING APPARATUS

In the mid-position, the bell of the spirometer exerts a static pressure not exceeding 2 mm. of water. The response of the spirometer to volume changes initiated by a mechanical pump of the piston type is shown in Fig. 2. There is a flat response over a range of 40 to 80 cycles per minute with a stroke of 3 L. The peak pressures under the bell during inspiration and expiration at various MBC are shown in Fig. 3. It is of interest to compare the pressures under the bell to peak pressures under the face mask at similar MBC as is shown in Fig. 4. The mask is attached to the spirometer by a piece of flexible tubing, 18 cm. long and 2.5 cm. in diameter at the narrowest portions. Of further interest is a comparison of the pressures beneath the face mask when attached to the Krogh spirometer to pressures beneath the face mask when the MBC is being measured through a conventional high velocity (Rudolph) valve and Douglas bag combination (Fig. 4). It is apparent from such comparison that the work imposed by internal resistance in the Krogh plus face mask combination is appreciably less than that in the high velocity valve plus Douglas bag combination. It would appear from these data that the instrument as

described will faithfully record single or summed excursions of the spirometer bell through cycle ranges apt to be met in clinical practice with less instrumental impediment to air flow than exists in some other conventional methods for measuring the MBC.

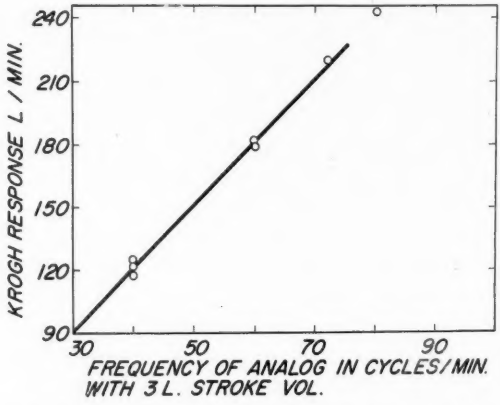

Fig. 2.—Dynamic response of spirometer and counter to mechanically controlled input.

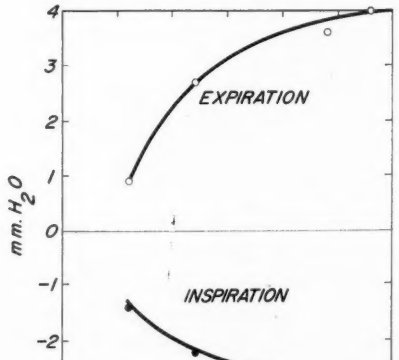

Fig. 3.—Peak pressure generated beneath the spirometer bell during various rates of MBC.

The frequency response of the direct writer is such that we do not believe the fluctuations in nitrogen concentration or stroke volumes faithfully represent the maxima of the true excursions. Although we do not know the precise degree of damping we have reason to believe that it is minimal. In these particular studies this failing is not of serious importance. Ample time for faithful recording of nitrogen concentration was provided in making the

terminal expiration and in measuring the concentration of nitrogen in the bag at the end of the run. As a further check, these values were read directly from the nitrogen meter.

COMPARISON OF MBC AND PULMONARY VOLUMINA AS MEASURED BY SIMULTANEOUS AND BY CONVENTIONAL METHODS

A group of normal individuals ranging in age from 17 to 50 years, and a similar group of persons having various degrees of diffuse obstructive pulmonary emphysema, were studied.

As seen in Table I, among normal and abnormal persons, there is a nice agreement between the average MBC as measured conventionally with a high velocity valve and Douglas bag and that measured in the optically recording Krogh spirometer. Both measurements are in close agreement with the mean of the predicted MBC for the normal group. In three instances, the difference

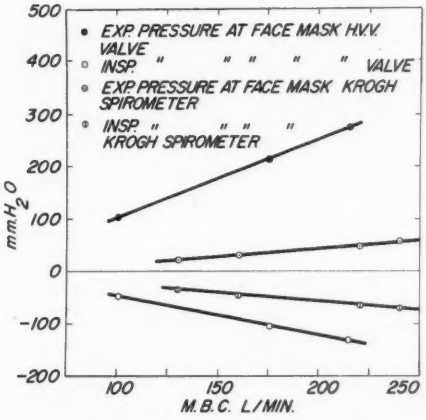

Fig. 4.—Peak pressure generated beneath face mask during various rates of MBC initiated by mechanical pump with stroke volume of 3 L. as measured by conventional high velocity valve and Douglas bag in contrast to the Krogh spirometer.

as measured by the two methods was greater than 10 L. in normal persons, while in abnormal persons it was never more than 5 L. There was a random scatter of all of the differences suggesting that the apparatus per se did not account for the variation. Some individuals found the Krogh spirometer to be more comfortable whereas others felt the reverse. We anticipated that the shorter connection between the face mask and the immobile spirometer would be a handicap and perhaps it was in some instances. No one complained of resistance in the apparatus used.

The vital capacity of both the normal and the abnormal individuals, as shown in Table I, was essentially the same when measured by the two spirometers. In 4 persons of each group the difference slightly exceeded 250 c.c. but was of a random distribution.

TABLE I. COMPARISON OF MBC AND PULMONARY VOLUMINA AS MEASURED BY THE NEW AND CONVENTIONAL PROCEDURES

	NO.	MEAN BY CONVENTIONAL METHOD	MEAN BY NEW METHOD	DIFFERENCES	MEAN OF DIFFERENCES	MEAN OF PREDICTED VALUES
			Normal Group			
MBC	16	158 L./min.	159	+1	7	152
V. C.	15	4.59 L.	4.52	−0.07	0.26	4.38
R. V.	17	1.13 L.	1.29	+0.16	0.19	1.28
T. C.	15	5.73 L.	5.80	+0.07	0.22	5.59
			Abnormal Group			
MBC	18	46 L./min.	45	−1	4	104
V. C.	11	3.21 L.	3.08	−0.13	0.28	4.04
R. V.	11	3.11 L.	3.01	−0.10	0.51	1.35
T. C.	11	6.31 L.	6.09	−0.22	0.68	5.39

The residual volume is estimated somewhat higher by the rapid method in normal persons as is shown in Table I. The maximum difference in any individual was 300 c.c. In no instance did the rapid method give an estimate significantly larger than the predicted normal figure. This degree of agreement is gratifying because we had anticipated the rapid method to estimate a higher residual volume than that obtained by the conventional method for the following reason. The accuracy of the closed circuit method, in contrast to the open circuit method, is strongly dependent upon the assumption that terminal expired nitrogen concentration truly represents the mean concentration of nitrogen in the lung as a whole at the moment of sampling. Distribution and mixing of inhaled gas is known to be imperfect even in normal persons during slow breathing. During rapid breathing this uneven distribution is augmented, the gas flowing preferentially to areas of lowest airway resistance and largest compliance. Because of this, the terminal expired sample may be obtained from the poorly ventilated area and hence be above the mean nitrogen concentration of the lung. A falsely high terminal expired nitrogen concentration leads to a falsely large residual volume. Of course, it is also possible that the major contribution to the terminal expired nitrogen sample may come from hyperventilated lung tissues. This will lead to a falsely low nitrogen and a falsely small residual volume. The advantage of the open circuit method is that the error caused by poor distribution is minimized because nitrogen is being constantly washed out and, over a 7-minute period, reaches a very low value except in grossly abnormal lungs.

Even in the abnormal group a reasonably good agreement was found between the two methods for measuring residual volume as shown in Table I. As might be anticipated from the above remarks, since uneven distribution and mixing are more severe in emphysematous than in normal persons, the difference between the estimates by the two methods is greater. It will be noted in Table I, that the mean of the differences between the two methods in the residual volumes of the abnormal group is almost three times as great as that of the normals. From a practical point of view, the residual volume cannot be estimated with reasonable accuracy unless equilibrium between the lung and bag is rather closely approximated. A further comment in this regard will be found in the conclusions.

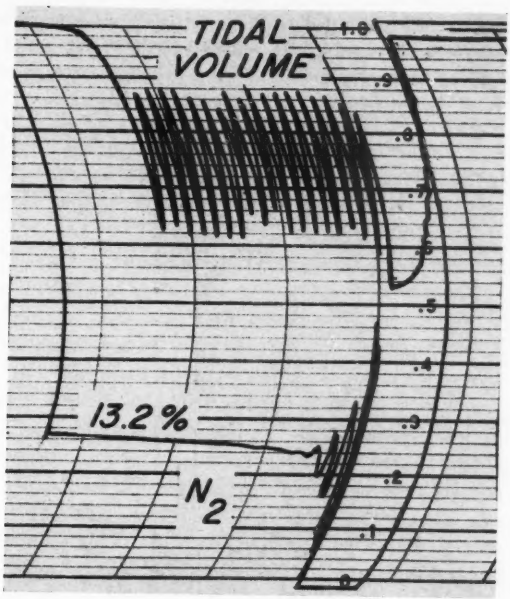

Fig. 5.—Tracing of tidal volume and of nitrogen concentration in rebreathed gas during MBC measurement in a normal person. Read from right to left. Inspiration has down stroke.

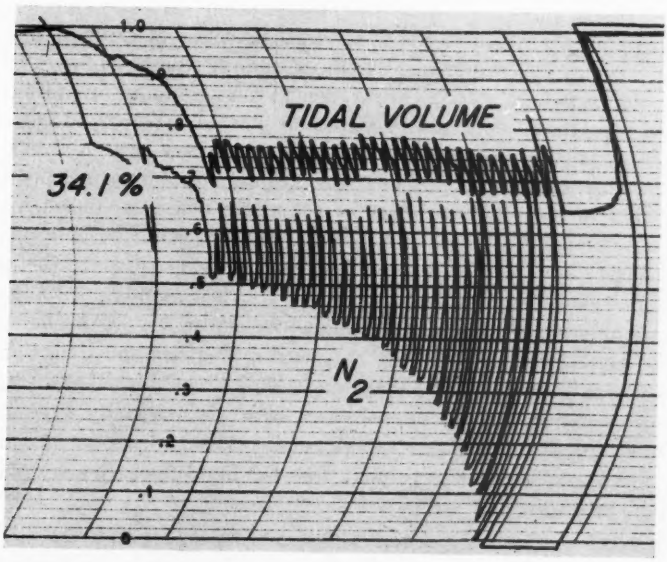

Fig. 6.—Tracing of tidal volume and of nitrogen concentration in rebreathed gas during MBC measurement in a case of diffuse obstructive emphysema. Inspiration has down stroke.

No discussion of the estimates of total capacity is needed since this is the sum of vital capacity and residual volume and the above remarks apply.

EFFECTIVE LUNG VENTILATION

In this study two methods were used for estimating effectiveness of lung ventilation. On the basis of inspection alone, it was apparent, as shown in Fig. 5, that the majority of normal persons achieved approximate equilibration in the lung and bag within three to six breaths during the maximum breathing capacity. No normal person required more than seven breaths to effect a nonfluctuating nitrogen concentration. A slight fluctuation undoubtedly occurred but could not be recognized with our equipment. In contrast, as shown in Fig. 6, each person of the abnormal group either failed to come to equilibrium or required more than ten breaths to do so. On the basis of inspection alone, one can separate a normal from an abnormal group. A second method involves the calculation of the theoretical number of breaths required to reach equilibrium based on the residual and tidal volumes. The normal individuals all actually reached equilibrium within one breath of the theoretical number while all of the abnormals required more than the theoretical number of breaths or failed to equilibrate at all. This portion of our study is still under investigation and will form the basis of a subsequent report.

CONCLUSIONS

Our original purpose in devising this equipment and applying the methods was to develop a procedure for the rapid screening of large populations in order to recognize those persons having normal ventilatory powers. Our data indicate that this unit will faithfully record the maximum breathing capacity and vital capacity in normal and abnormal persons. The rapid closed circuit method of measuring residual volume is subject to some error, but is acceptable as a screening procedure for separating normal from abnormal persons. We suggest that in those persons who do not attain nitrogen equilibrium during the maximum breathing capacity, better accuracy could be obtained by permitting them to continue to rebreathe at a lower rate after the maximum breathing capacity has been performed. The test could be prolonged until equilibration is approximated, and in this way expiratory elevation of nitrogen would be minimized. This would, of course, lengthen the time for the procedure. There appears to be a sharp division between normal and emphysematous persons in the number of maximum breathing capacity type of breaths required to produce nitrogen equilibrium. Although quantitation of this impairment is not possible at present, the striking difference suggests a useful screening procedure.

Since diffuse obstructive emphysema is characterized physiologically by a subnormal MBC, elevated residual volume and abnormal lung rinsing (distribution, mixing, and tidal volume to residual volume ratio), the apparatus and methods described might be expected to recognize preclinical stages of

the disease. In addition, quantitation of the ventilatory impairment can be obtained. Direct reading of the MBC and vital capacity, and the use of a nomogram for calculating residual volume facilitate the speed of measurement.

SUMMARY

1. A direct reading spirometer is described and dynamically evaluated.

2. A method for simultaneous measurement of MBC, pulmonary volumina, and effective lung ventilation is described and compared to conventional measurements for the same estimates in normal and emphysematous persons.

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(For Discussion, see page 703.)

AN ACRYLATE-AMIDE FOAM ARTERIAL PROSTHESIS

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INTRODUCTION

DUE to the complex nature of the difficulties involved, it does not seem likely that prevention of degenerative or congenital lesions of the vascular system will be achieved in the near future. It is probable that traumatic lesions will always require surgical management. Therefore, arterial repair and replacement are and will continue to be lifesaving restorative procedures. It is the aim of this investigation to devise a more satisfactory prosthesis to accomplish this replacement. A review was made of previous experiments in arterial replacement.[1-68] The factors involved in the success or failure of these experiments provided insight as to the qualifications of an ideal arterial prosthesis. This review was coupled with a study of the physical characteristics of normal human arteries. From these studies the characteristics of an ideal arterial prosthesis are derived. These are: (1) be nontoxic, noncarcinogenic, nonallergenic, (2) incite little inflammatory or foreign body response, (3) have capacity for intimization with incorporation by fibrous ingrowth, (4) have strength to withstand arterial pressure indefinitely, (5) be initially porous with ability to become rapidly impervious to blood, (6) be elastic and flexible, (7) be easily inserted, (8) have a smooth internal wall, (9) be easily sterilized and stored, and (10) be easily manufactured at a nonprohibitive price. In addition, studies of normal arteries reveal that "the smooth muscle—elastic tissue network responsible for the aortic retractile force over a rather wide range of distension shows mechanical and thermal properties often associated with rubber."[69] To meet this requirement of elasticity, the search for a more ideal prosthetic material was limited to the elastomers. Of this group of materials, Kel-F† elastomer and an acrylate-amide elastomer‡[70] developed at the Army Prosthetics Research Laboratory were

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*Army Prosthetics Research Laboratory, Walter Reed Army Medical Center.

†Manufactured by the Minnesota Mining and Manufacturing Company, St. Paul, Minn.

‡Acrylate-amide elastomer is a polyacrylic ester rubber; a terpolymer of butyl acrylate (90 parts), methyl methacrylate (7.5 parts) and methacrylamide (2.5 parts) with ethyl methacrylate filler (37 parts).

selected because of their quality of inertness. Subsequent to their selection, two new elastomers, Hypalon* and Viton,* having potentially similar desirable qualities, have become commercially available.

To achieve ease of handling and rapid intimization with minimal initial bleeding after insertion, a foam construction was selected for the prosthesis. Considerable difficulty has been encountered in the development of a foam of proper pore size and consistency from these elastomers. This has been accomplished to date with the acrylate-amide elastomer.

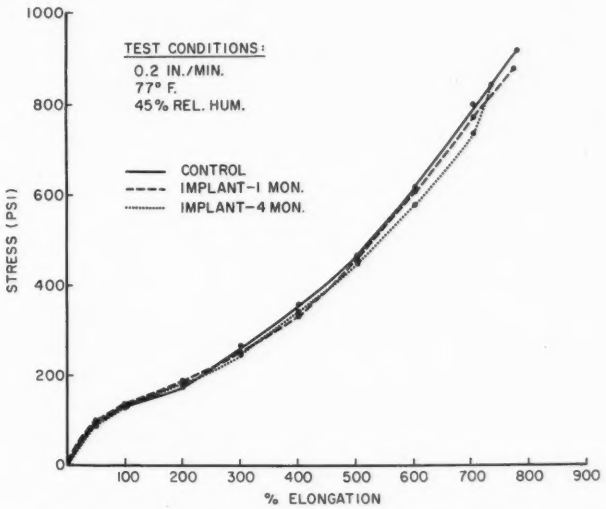


Fig. 1.—Stress-strain curves for acrylate-amide films implanted subcutaneously in dogs for 1 and 4 months. Instron testing machine.

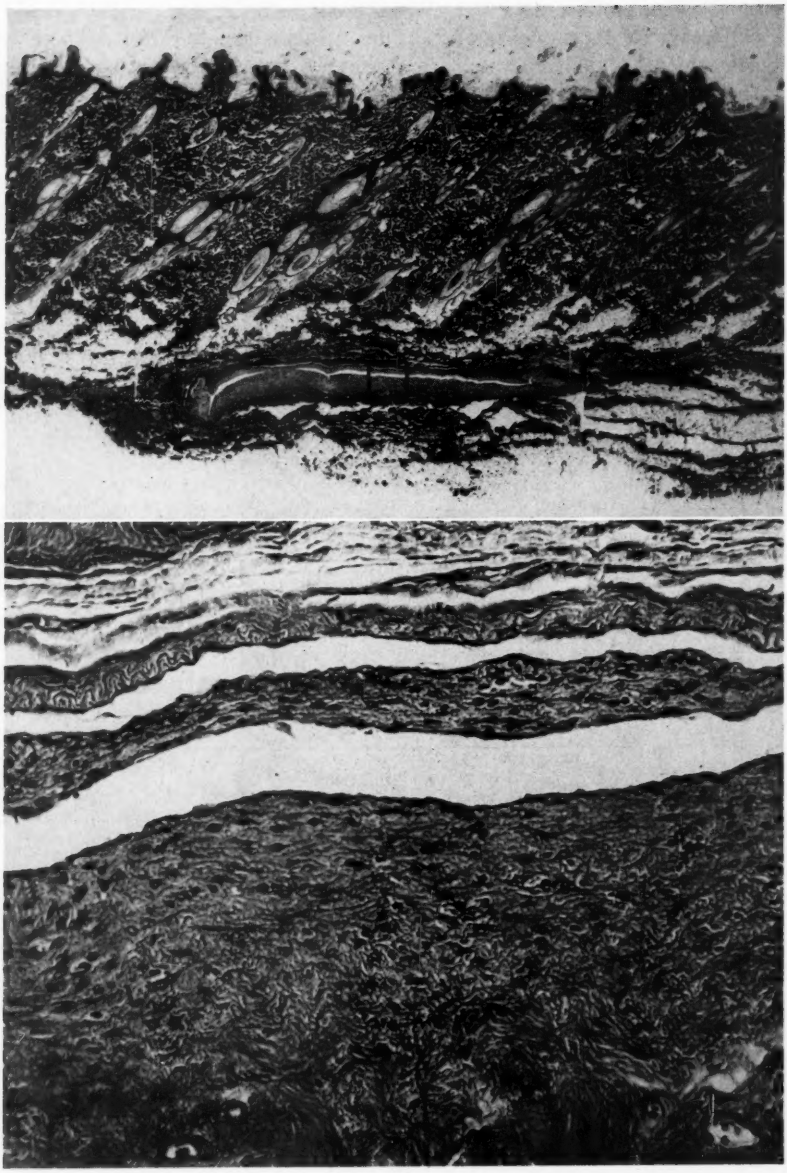
EVALUATION OF PHYSICAL PROPERTIES

The inertness of acrylate-amide elastomer was evaluated by analysis of stress-strain deviation after implantation and by tissue reaction. Die-cut strips of cast acrylate-amide film were implanted in the subcutaneous tissue of dogs. These strips were removed at intervals of 1 and 4 months after implantation, and were tested by stress-strain analysis against control samples. The results of this test are graphically illustrated in Fig. 1. No measurable degradation appears to have occurred in the acrylate-amide elastomer during the time of implantation. Long-term studies are being made to determine whether degradation will occur on extended exposure to body fluids.

Similar die-cut strips of acrylate-amide film and foam were inserted subcutaneously in dogs and removed at 1-, 4-, and 5-month intervals to evaluate tissue reaction. The elastomer was grossly well tolerated without extrusion or fluid collection. Microscopic study of the tissue adjacent to the implanted

*Manufactured by E. I. Dupont de Nemours & Co., Inc., New York, N. Y.

A.

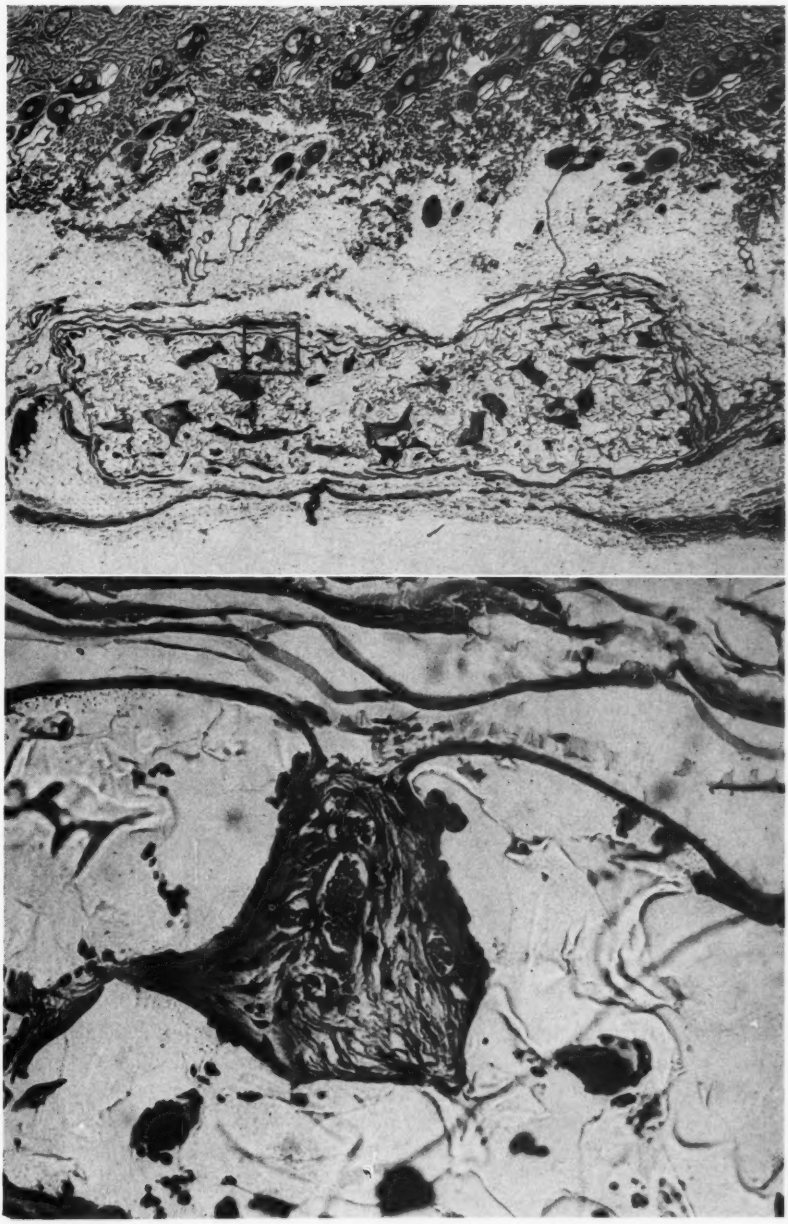


B.

Fig. 2.—*A*, Site of implantation of acrylate-amide film in subcutaneous tissue, 4 months' duration. The film has been removed. Blocked area is shown in higher magnification. (Rinehart ×16; reduced ½.)

B, Marginal cellular reaction consists mainly of fibroblasts. Occasional lymphocytes are apparent and, in the deeper parts, endothelial elements. Note absence of necrosis, foreign body type giant cells, and polymorphonuclear leukocytes. (Hematoxylin and eosin ×234; reduced ½.)

A.



B.

Fig. 3.—*A*, Acrylate-amide foam implanted for 4 months in the subcutaneous tissue of a dog. Small scattered granulation tissue buds are visible. Note scanty marginal reaction to foam as compared to film. Blocked area is shown in higher magnification in *B*. (Rinehart ×16; reduced ½.)

B, Ingrowth of connective tissue into acrylate-amide foam. Granulation tissue bud is composed of fibroblasts and endothelial elements with occasional formed capillaries. Some histiocytes and occasional lymphocytes are apparent also. (Hematoxylin and eosin ×234; reduced ½.)

material revealed connective tissue proliferation about the film (Fig. 2) and into the foam (Fig. 3). The cellular reaction to the material was very slight and consisted of occasional lymphocytes, histiocytes, and rare polymorphonuclear leukocytes. No multinucleated giant cells were found and there was no evidence of necrosis; findings which one might expect with chemical irritation or inflammation.

The fabrication of the foamed elastomer into tubular forms and flat sheets was made by forming foamed acrylate-amide elastomer over a glass mandril.

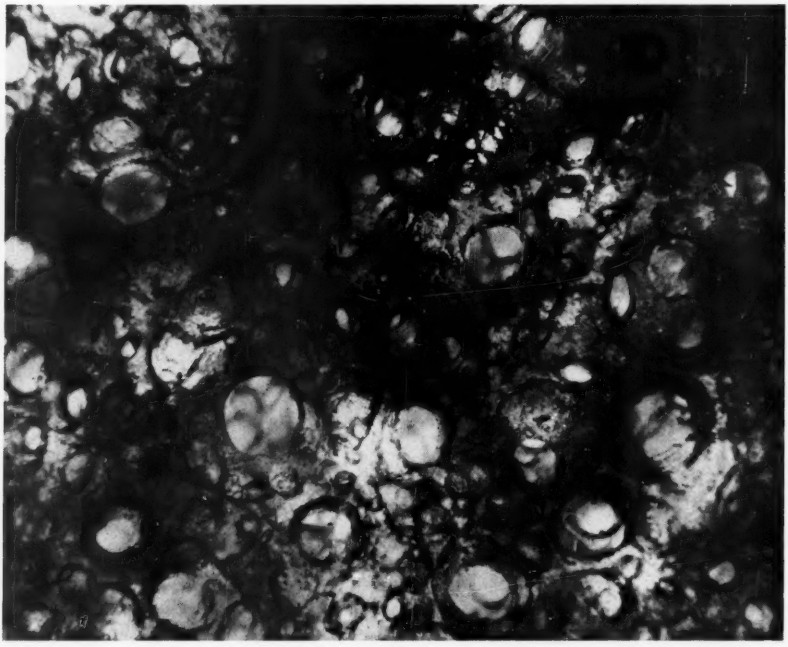
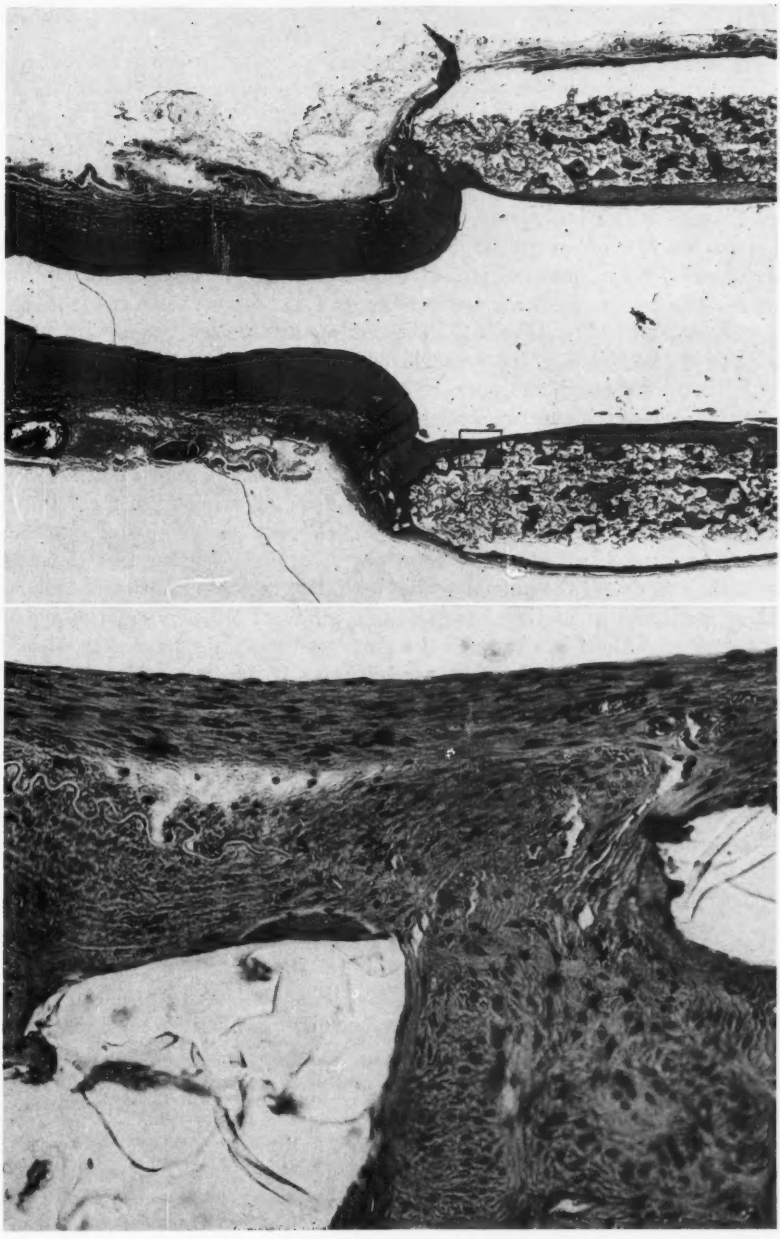


Fig. 4.—Photomicrograph of acrylate-amide foam showing open-cell structure. (×32; reduced ½.)

Optimal pore size was determined by a pilot experiment using Ivalon prostheses of varying known pore sizes and, finally, by trial and error with the acrylate-amide elastomer. Pore size of our present prosthesis varies from 30 to 600 μ with a mean of approximately 250 μ and may be altered to meet varying intravascular pressures (Fig. 4).

Because the tensile strength of a foam is inherently variable, rupture occurred in some of the early model prostheses. Therefore, the prostheses were reinforced with a porous woven tube of two-way stretch Dacron fabric by bonding the tube to the inside of the graft in the foaming process. This has not altered the elasticity of the foam prosthesis. Tensile strength of the woven Dacron reinforcement is 42 pounds per linear inch of cloth.

A.



B.

Fig. 5.—*A*, Longitudinal section of unreinforced acrylate-amide abdominal aortic graft removed from dog at 8 weeks. Blocked area is shown in higher magnification in *B*. (Hematoxylin and eosin ×7.1; reduced ½.)

B, The internal elastic layer of the aorta is visible in the left half of the figure, and the overlying intima shows slight to moderate thickening. The intima of the aorta merges imperceptibly with the intima of the graft. (Hematoxylin and eosin ×234; reduced ½.)

EXPERIMENTAL LABORATORY APPLICATION

Twenty-two segments of abdominal aorta and seven superficial femoral arteries of dogs have been replaced by acrylate-amide foam prostheses. The internal diameter of the aortas varied from 5 to 8 mm. while that of the femoral artery segments varied from 2.5 to 4.5 mm. Four dogs have been sacrificed, 1 at 4 weeks, 2 at 8 weeks, and 1 at 12 weeks. All arteries removed at sacrifice were patent. A follow-up on the remaining twenty-four prostheses is being carried out for the effects of long-term use. To date, all are patent. Intimization of our present prosthesis is complete by 8 weeks and has a mean thickness of approximately 280 μ (Fig. 5). The rate of intimization varies with porosity and was not complete by 12 weeks in an early model prosthesis of small pore size. Bleeding through the pores of the prosthesis is moderate and terminates in 5 to 20 seconds without preclotting. The average estimated blood loss through the interstices of an abdominal aortic prosthesis of 3 to 4 cm. in length is 10 c.c.

Acrylate-amide foam sheets reinforced with Dacron fabric have been implanted in the pulmonary outflow tract of 4 dogs. A segment of right ventricle and pulmonary artery was grasped in a partial occluding clamp and an elliptical defect was created in the wall of the right ventricular outflow tract, extending across the annulus of the pulmonary valve. The graft was inserted in the defect and sutured with a running, over-and-over stitch of 5-0 polyethylene monofilament suture.* Blood loss through the graft was minimal. One of the dogs was heparinized with 1.0 mg. heparin per kilogram at the time of insertion of the prosthesis. The prosthesis was not preclotted. Upon release of the clamps, bleeding through the prosthesis was minimal and stopped after 1½ minutes of digital pressure. Estimated blood loss was 15 c.c. All dogs tolerated the procedure without complication. One dog was sacrificed at 1 month to ascertain degree of intimization, which was found to be complete. The remaining 3 dogs will be kept for long-term study.

DISCUSSION

A new arterial prosthesis has been fabricated, possessing characteristics which approach our criteria for the ideal arterial prosthesis. It is made of a new terpolymer, an acrylate-amide elastomer, which has been shown to incite little inflammatory or foreign body response. It is nontoxic and, in the foam state, capable of being incorporated in the body tissues by ingrowth of fibrous tissues. The outstanding characteristics of the acrylate-amide prosthesis are its ease of handling, suturing, and insertion. The resiliency of the foam is such that anastomosis is accomplished with little if any bleeding at this site. The graft can be cut at any angle without fraying. Because of its foam construction, bleeding through the interstices is slight, although pore size is sufficiently large to permit early ingrowth of fibrous tissue and rapid intimization.

The prosthesis can be fabricated with varying degrees of elasticity and its flexibility is maintained after implantation. It has a smooth internal wall and

*Linear monofilament polyethylene suture. For investigational use by Davis and Geck, Surgical Products Division of the American Cyanamide Co., New York, N. Y.

has been used successfully to replace vessels having an internal diameter as small as 2.5 mm. Repeated autoclaving causes no degradation of the plastic nor loss of tensile strength.

Manufacture at this time is on a laboratory scale but techniques of fabrication are being improved. As yet, complex shapes (bifurcations and arches) have not been produced.

SUMMARY

An arterial prosthesis has been developed utilizing a Dacron fiber reinforced foam of a new acrylate-amide elastomer. Laboratory application leads to the impression that this prosthesis will make feasible more successful replacement of arteries of small diameter.

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(For Discussion, see page 703.)

EXPERIMENTAL OBSERVATIONS ON POST-STENOTIC DILATATION

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A MOST puzzling phenomenon encountered in medicine is the dilatation of a vessel downstream from a stenosis. Though not universally found, it is sufficiently common to be looked for when aortic or pulmonic stenosis, or coarctation of the aorta is being considered (Fig. 1). A striking feature is that post-stenotic dilatation may occur in a region where a relatively low pressure exists.

In cases associated with congenital defects, an accompanying weakness of the adjacent vessel wall might lead to dilatation. However, its failure to develop in a high pressure region upstream, in the case of coarctation, is difficult to explain without assuming that the weakness of the congenital vessel wall is peculiarly restricted to the downstream region. Futhermore, it is seen with acquired valvular stenosis, which does not strengthen this hypothesis. Last, it can be produced easily in the healthy vessel walls of experimental animals.[1, 2]

Our original interest lay not in the cause of post-stenotic dilatation, but in the cause of murmurs. This led to a better understanding of the fluid mechanics of blood flow, and this knowledge has been applied to post-stenotic dilatation.

By reviewing the factors involved in the production of murmurs, it was found that the classic theory that murmurs are due to turbulence is an unreasonable one. A new theory was proposed which attributed murmurs to nearly periodic pressure fluctuations in the wake downstream from an obstacle or constriction.[3] These fluctuations develop in response to the shedding of vortices and are of a magnitude large enough to produce audible sound. The basic mechanism is that found in the production of Aeolian tones. Because of the lack of symmetry and smoothness around or through which blood must pass, the pressure fluctuations are not strictly periodic. As a result, noise rather than a clear tone is produced. However, the same order of acoustical efficiency is realized. The discrete pressure fluctuations are of an intensity much greater than those one would expect from turbulence.[4] As such, they are better generators of noise.

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One of the characteristics of periodic or nearly periodic wakes is that most of the energy which this type of flow produces is concentrated in the region immediately downstream from the obstacle or constriction; and, thus, one would expect murmurs to be most intense in this region. This expectation is realized both in experimentally induced stenosis as well as in one's ability to localize murmurs clinically. If this is true for murmurs so also must it be true for thrills, and one would expect the vessel wall vibrations of a thrill to be maximal in intensity a short distance distal to the stenosis. It was then postulated that the damage resulting from these local vibrations may so affect

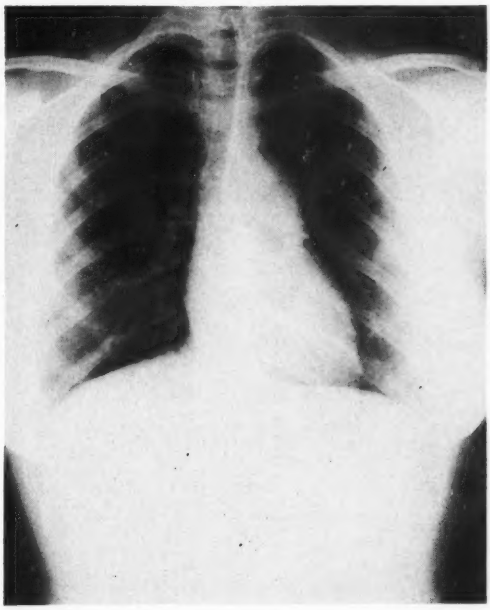

Fig. 1.—Preoperative chest x-ray film of a 10-year-old girl with congenital valvular pulmonic stenosis and considerable dilatation of the pulmonary artery segment. Right ventricular and pulmonary artery pressures were 141/8 and 14 (mean) mm. Hg. Fifteen months postoperatively the right ventricular pressure had fallen to 40/4 mm. Hg and the mean pulmonary artery pressure remained the same. There was no change in the chest x-ray film. (Patient of Drs. R. Gross, H. Hultgren, F. Eldridge, and F. Gerbode.)

the vessel wall that structural fatigue would ensue. If so, this could lead to dilatation even in a region of low pressure. Our experiments were designed to test this hypothesis (Fig. 2).

METHODS AND RESULTS

It was desirable to use elastic tubes so as to approximate the structure of vessel walls in which post-stenotic dilatation is encountered. These tubes should be thin-walled so that any structural fatigue will be manifested in a relatively brief period of time. The latex rubber tubing used as Penrose drains served admirably.

These tubes were filled with water and a static pressure was maintained. They were plugged with rubber stoppers at both ends so that no flow could take place. Through one of the stoppers a vibrating blade was inserted. This was driven by a pipette shaker (Fig. 3). The amplitude of the oscillations was maximal at the tip of the blade. The vibrating rate was determined

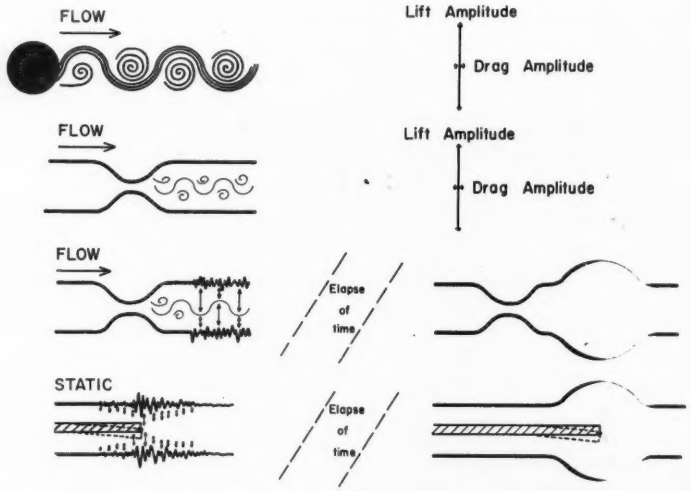

Fig. 2.—Diagram of the theoretical basis of the production of murmurs, thrills and post-stenotic dilatation. With flow past a wire or cylinder, vortices are shed which cause periodic pressure fluctuations in the wake. The bulk of the energy is radiated in a direction perpendicular to the flow (the lift amplitude) rather than parallel to the flow (the drag amplitude). Flow through a stenosis is a modification of this basic pattern. The energy of the pressure fluctuations is of the order of acoustical intensities and, if strong enough, will be transmitted to the vessel wall, causing it to vibrate. With time this could lead to structural fatigue of the elastic tissue, with dilatation the result. Experimentally, a vibrating blade can reproduce these physical forces. By using a static tube, physical forces due to fluid flow can be eliminated and the effectiveness of vibrational fatigue more clearly tested. In practice, the point of maximal vibration of the tubing wall was usually found to be 0.5 cm. proximal to the blade tip.

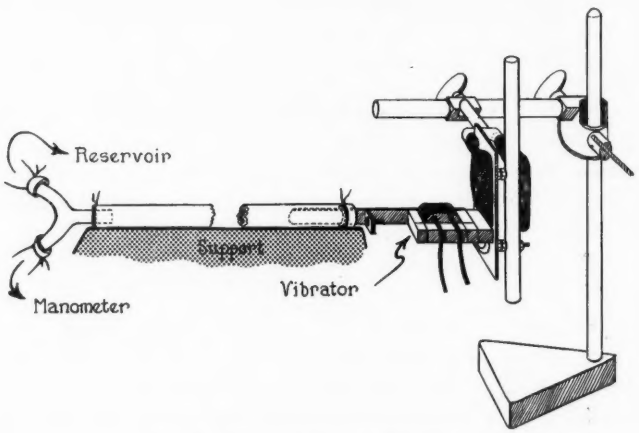

Fig. 3.—Diagram of apparatus used.

by stroboscopic illumination and was found to be 96 cycles per second. The blade was so placed that it did not touch the tubing wall. Thus, the energy of the vibration was transmitted through water to the elastic walls. The region of maximum vibration was found to be approximately 0.5 cm. proximal to the blade tip. Thus, all but two factors that may cause wall damage were eliminated. Only a hydrostatic pressure load and periodic pressure fluctua-

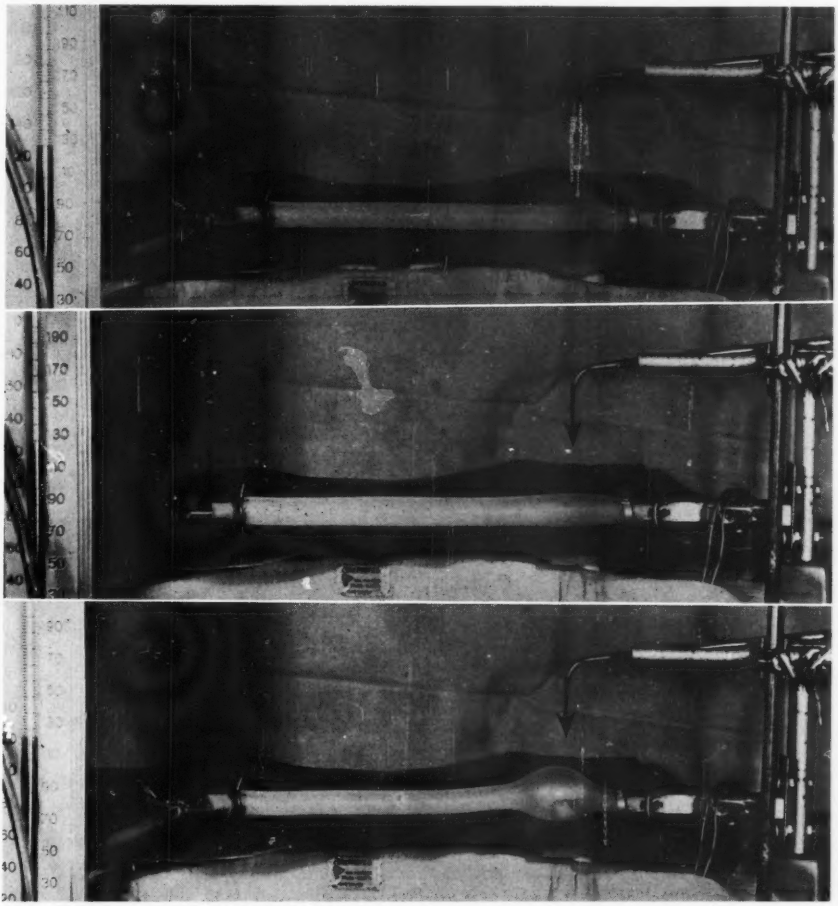

Fig. 4.—The tube after (*A*) 1 hour of vibration, (*B*) 8 hours of vibration, and (*C*) 10 hours of vibration; the tubing wall is weakened to the degree that it can no longer support the original hydrostatic pressure load of 130 mm. Hg.

tions, roughly of the magnitude of acoustical intensities, were the forces applied. This arrangement, we felt, approximated the physical factors to be tested which are found in the region in which post-stenotic dilatation occurs.

Ten tubes, of varying quality, were placed under constant hydrostatic pressure which varied from 130 to 140 mm. Hg. After from 7 to 120 hours,

a moderate dilatation was noted in the tubing wall in the region subjected to vibration. Within 5 hours after this occurred, the stressed segment was unable to withstand the original hydrostatic pressure and progressive dilatation was noted (Fig. 4). It was discovered that the higher static pressures led to earlier dilatation.

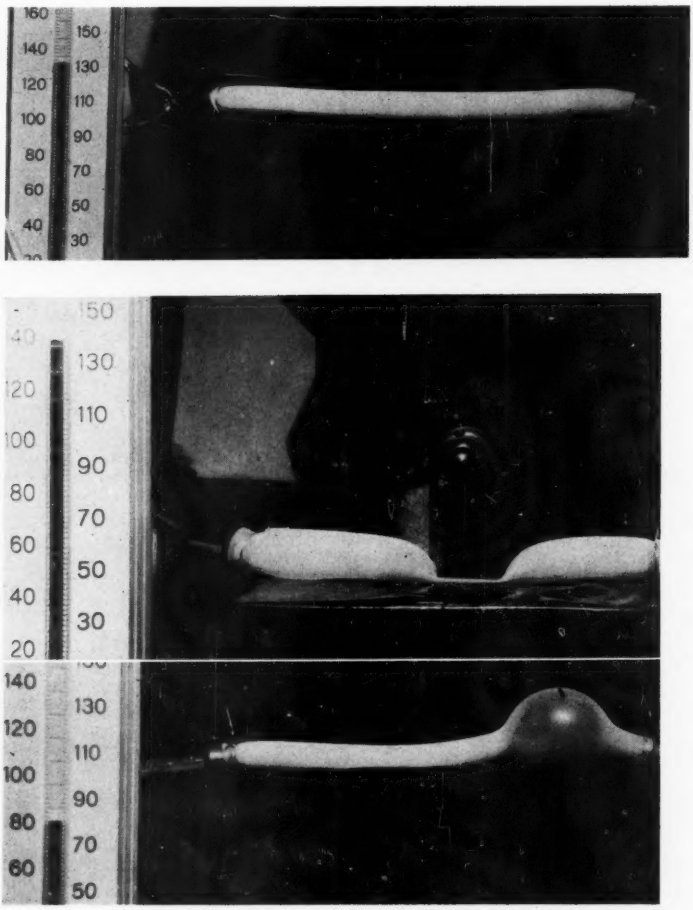

Fig. 5.—*A*, Tube under static pressure of 135 mm. Hg after 185 hours. *B*, Tube during compression after 65 hours. *C*, Tube after 30 hours of vibration; the original pressure load was 130 mm. Hg. A line marks the point of maximum vibration.

Five tubes, not subjected to vibration, were placed under very high hydrostatic pressures. These ranged from 190 to 240 mm. Hg. At these pressures, the strength of the material would be exceeded and dilatation would occur at one or the other end of the tube. It was noted that this dilatation occurred at a distance of from 2.25 to 3.5 cm. from the point of fixation. The fact

that the tube dilated at this constant location suggested that fixation of the tube had some part to play in the site of weakening. However, the vibrating blade was so placed in the ten tubes previously mentioned, that the point of maximum vibration was 4 cm. or more from the point of fixation.

To exclude further the possibility that the tube with time would have dilated at this point without vibration the following modifications were made. The vibrating blade was lengthened until the point of maximal vibration could be felt at a point 9.5 cm. from where the tube was fixed about the stopper. After 10 hours, dilatation occurred at this point. We were unable to extend the length of the blade beyond this point as nodes developed which gave several points of nearly equal vibration and thus did not permit a concise experiment.

In order to test the relative effect of the various factors that may be involved in post-stenotic dilatation, the following experiment was performed. Short segments of tubing from adjacent areas were cut. One segment was subjected to a static pressure of 135 mm. for 185 hours without the appearance of dilatation. Another tube was compressed by a plunger, and the pressures in this tube varied from 138 to 142 mm. Hg at maximum compression. This is not a wide range of pressures; however, the short segment

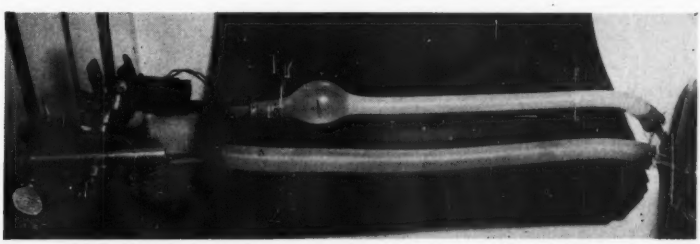

Fig. 6.—Matched tubes after 104 hours. Upper tube was subjected to vibration. A line marks the point of maximum vibration. The lower tube, not subjected to vibration, did not show local dilatation after 2 weeks.

of tubing was found to dilate 2.3 mm. Hg during each compression stroke, representing considerable stretch. After 65 hours no dilatation was noted. A third segment was subjected to 130 mm. Hg and, after 30 hours of vibration, dilatation was observed at the point of maximum vibration (Fig. 5).

Because of the wide range of time required to produce dilatation, tubing produced by one manufacturer (Duval) was used in the last experiment. Matched sections were cut from the middle of the standard 90 cm. lengths. Each pair of tubes was placed under the same hydrostatic pressure load. One of the pair was subjected to vibration, the other was not. Four tubes at from 135 to 140 mm. Hg dilated at the point of maximum vibration in from 73 to 115 hours. The respective pairs showed no dilatation after 2 weeks (Fig. 6). Another tube at 130 mm. Hg dilated after 580 hours of vibration. A matched section at the same pressure did not dilate after 2 months. This experiment demonstrated that the vibratory stress appears to be the one of greatest significance.

DISCUSSION

Many theories have been proposed which have sought to explain the development of post-stenotic dilatation on the basis of physical principles. Campbell and Kauntze[5] have postulated that post-stenotic dilatation in aortic stenosis can be largely explained by the relative elevation of lateral pressure in the region downstream from the stenosis (the Bernoulli principle). They recognized, however, that the very low downstream pressure in pulmonary stenosis made this explanation less plausible. They also felt that the presence of post-stenotic turbulence may be another factor in the development of post-stenotic dilatation.

Holman[1] was the first to submit the question of post-stenotic dilatation to exhaustive physical analysis. He emphasized the importance of considering the factors of physical stress which lead, in time, to structural fatigue of the vessel wall. He felt that the high velocity jet of blood issuing from the stenosis was suddenly retarded by the slow moving stream distal to the stenosis, causing a local conversion of kinetic energy into lateral pressure. In addition, this process led to the development of eddies of turbulent flow and reversed flow which struck the vessel wall and led to its vibration. He felt that the sites of the production of a local high lateral pressure and greatest turbulence were the same, and that at this place the point of maximum dilatation was found.

Robicsek[6] and his colleagues studied the problem and could find no experimental or clinical evidence of a "local increase" of the lateral pressure in the post-stenotic region. By injecting dye into a glass model of a stenosis with a post-stenotic dilatation, they demonstrated that there was maximum turbulence in the distal end of the dilated region (Holman, by the same technique, had also demonstrated the presence of turbulence in the area of post-stenotic dilatation). They felt, then, that turbulence was an acceptable explanation of the weakening of the vessel wall and the consequent development of post-stenotic dilatation. However, they accepted the "possibility that the cavitation process is perhaps the most important factor in producing the anatomic phenomenon known as poststenotic dilatation by injuring the wall of the blood vessel."

It is difficult for us to understand why a model of already existing post-stenotic dilatation was chosen to demonstrate the presence of turbulence. This may have been the cause of Robicsek's dye injection study showing that the region of maximal turbulence is not at the site of maximal dilatation but, rather, at the point where dilatation has decreased to almost the normal vessel caliber. Be that as it may, the theory that turbulence could lead to post-stenotic dilatation appears even less likely when one realized that it is very probably incapable of producing pressures even of the order of acoustical strength. To ask that turbulence set the vessel wall into vibration seems to be an unreasonable demand.

When, however, one considers that the wake in blood can be made to fluctuate pressure-wise in a nearly periodic fashion due to the presence of an obstacle or narrowing in the vessel wall, then it appears reasonable that a force is present capable of producing a murmur. If large enough, this force

will be manifest as a thrill. It appeared to us that this was the factor to investigate, as of all the possible sources of unusual stress on the downstream wall of the vessel, the murmur (and thrill) is the only one present, and present in maximal intensity, in the region in which one notes post-stenotic dilatation. In this connection, Spencer[7] and his colleagues have shown that murmurs of coarctation, recorded directly from the aorta, are maximal in intensity in the region of greatest post-stenotic dilatation.

In regard to the question of cavitation, it should be briefly noted that work in this laboratory has shown that it will not occur in blood unless the driving pressure is at least 350 mm. Hg. As pressures of this magnitude are rarely, if ever, encountered in the body it seems that this is an unlikely explanation of post-stenotic dilatation.

These experiments were performed with thin-walled rubber tubes and with energies which approximated those which might be found with a loud murmur and a moderately intense thrill. It may be that the relatively thick-walled vascular structures would be able to withstand these stresses and not tend to dilate. This report, however, suggests that vibration of discrete segments of distended elastic tubes can lead to dilatation in that area. The fixation of the tubes to a solid surface undoubtedly contributes to the dilatation, but appears to be less significant than vibration.

It is hoped that this work has offered a satisfactory physical basis for post-stenotic dilatation consistent with the known physiologic and clinical characteristics of the phenomenon.

SUMMARY

The physical factors which may play a part in the development of post-stenotic dilatation are re-examined. Factors relating to pulsatile flow are found to be unlikely causes. A new theory of murmurs is applied and the hypothesis is made that vibrations of the vessel wall (thrills) are of sufficient energy to cause structural fatigue and dilatation. This was demonstrated by subjecting latex rubber tubes held under a static pressure to vibration.

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(For Discussion, see page 703.)

THE PATHOLOGIC EFFECTS OF METALLIC FOREIGN BODIES IN THE PULMONARY CIRCULATION

A Long-Term Experimental Study

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INTRODUCTION

THE SURGICAL management of the asymptomatic metallic foreign body lodged in the pulmonary arterial circulation poses a difficult problem because of the paucity of reports and diversity of opinion. However, it is probable that this condition is not as rare as is recorded for we know of several unreported cases. When hemorrhage or infection is present there is a clear-cut indication for the removal of the foreign body. Yet when the foreign body is asymptomatic and has produced no significant pulmonary changes on the chest roentgenogram, the advisability of a thoracotomy to remove this foreign body is open to question. We have been faced with this problem clinically and it is possible in one instance that we removed a foreign body from a branch pulmonary artery unnecessarily. Since World War II, potential infection, hemorrhage, emboli, and septicemia have been cited as indications for removal of the asymptomatic foreign body. Considerable support for this point of view may be found in the medical literature.[1, 5, 8, 9, 10] The justification for the prophylactic removal of asymptomatic foreign bodies has been based on what seems to be logical theoretical considerations. However, except for sporadic cases, neither long-term clinical nor experimental studies concerning the fate of foreign bodies in the pulmonary arteries are available.[2, 6] Thus, this series of experiments was undertaken to determine ultimate effects of metallic foreign bodies introduced into the pulmonary arterial circulation and the systemic circulation of mongrel dogs under varying conditions up to a period of 2 years.

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METHOD

A total of 66 foreign bodies was introduced into the superior vena cava or directly placed in the main pulmonary artery in 42 mongrel dogs (Table I). To compare the reaction of the pulmonary artery to that of systemic

TABLE I. INTRAVASCULAR FOREIGN BODIES

SITE	NO. OF FOREIGN BODIES	NO. OF DOGS	MORTALITY
Right atrium	4	4	0
Right ventricle	1	1	0
Main pulmonary artery	8	7	4
Branch pulmonary artery	53	28	1
Common iliac artery	14	14	0
Totals	80	42	5

vessels, a series of 14 metallic foreign bodies were introduced into the common iliac arteries of dogs. Large mongrel dogs weighing from 15 to 35 kilograms were employed. Lead fragments from 15 to 20 mm. in longest dimension, 22- and 38-caliber lead bullets, and fragments of needles were used.

Employing positive pressure ether anesthesia, the chest was opened under aseptic conditions. Lead bullets and fragments were then introduced into either the superior vena cava or the main pulmonary artery. In some of the animals the foreign bodies were introduced into the common iliac arteries immediately following the completion of the thoracotomy. Roentgenograms and gross and microscopic studies of the effects of the foreign bodies were made at periods of time varying from the day of operation up to 48 months.

RESULTS

Fate of Foreign Bodies Introduced Into the Superior Vena Cava.—

At the beginning of our experiments, foreign bodies to produce pulmonary embolization were introduced directly through the azygos vein into the superior vena cava and forced into the right atrium. This method was chosen since it is the usual manner in which foreign bodies enter the pulmonary circuit. After a study of 15 such experiments, we found, in a third of the cases, the foreign body lodged in the right atrium or right ventricle and two thirds of them lodged in the pulmonary arterial circulation. The foreign bodies in the right side of the heart were well tolerated.[6] By the third week they were completely covered with endothelium and caused no erosion or embolization in observations extending over 20 months.

Pulmonary and Systemic Arterial Reaction to Foreign Bodies.—

In none of the 61 instances in which a foreign body was introduced into the pulmonary artery and in the 14 times that a foreign body was introduced into the common iliac artery did erosion of the vessel, secondary hemorrhage, or infection take place (Table II). In the pulmonary artery, minimal clotting

TABLE II. REACTION OF PULMONARY AND ILIAC ARTERIES TO METALLIC FOREIGN BODIES

	NO.	EROSION	PROXIMAL CLOT	DISTAL CLOT
Main pulmonary artery	8	0	0	0
Branch pulmonary artery	53	0	0	0
Common iliac artery	14	0	6*	6*
Totals	75	0	6*	6*

*Slight.

occurred the first 2 or 3 days after the injection of a foreign body but no massive clotting occurred either proximal or distal to the foreign body. There was a rapid encasement of the foreign body by organization of the clot and growth of the intima of the vessel to cover the ends of the foreign body which

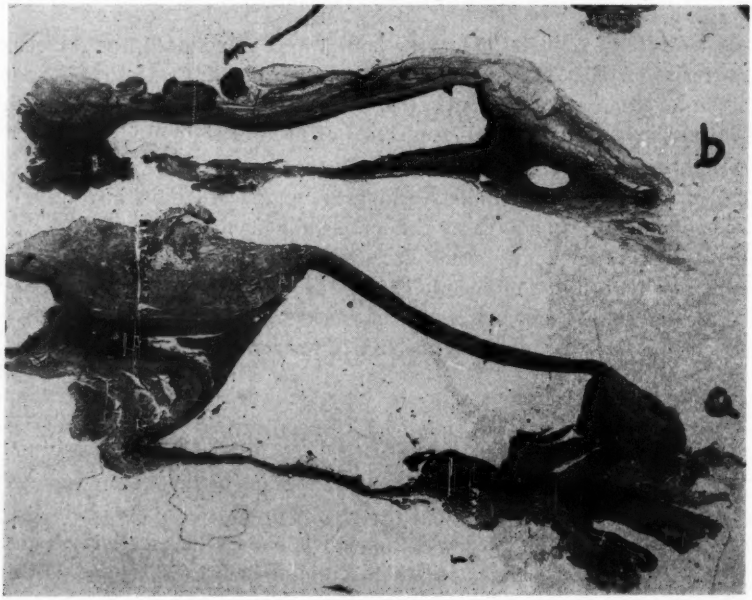

Fig. 1.—Dog 478. Longitudinal low-power section of left main pulmonary artery and right common iliac arteries 3 days after embolization of lead foreign bodies. *a*, Left main pulmonary artery. *b*, Left common iliac artery. Both vessels show early organization of small clot proximal and distal to the foreign body.

was encased in this fibrous cocoon or capsule. This reaction, which we have not found reported before, appears to be similar to that shown by the growth of endothelium in the lining of vessel substitutes. In the common iliac artery in dogs, there is an excellent collateral blood supply due to the fact the dog has an additional large caudal artery extending from the mid-portion of the bifurcation of the aorta downward. Foreign bodies in the common iliac arteries of dogs showed a response to the foreign body similar to that observed in the pulmonary artery. This reaction is due to the fact that there is an excellent collateral circulation preventing massive clotting distal to the

foreign body. The bullet is well encased in 10 days' time, and shows very little change in periods of observation up to 2 years.

Fig. 1, *a* shows a pulmonary artery 8 days after the implantation of a 38-caliber lead bullet. The reaction is similar to that presented in Fig. 1, *b*, which shows the common iliac artery where a 22-caliber bullet was lodged. Three days after implantation, one notes early organization of the clot. By the end of the second week the fibrous capsule is complete and thereafter shows very little change. Fig. 2, *a* shows a low-power photograph of the pulmonary artery, 18 months after implantation of a foreign body. Comparable findings are seen in Fig. 2, *b*, which shows the reaction to a foreign body in the common iliac artery implanted 18 months previously. In both instances the foreign body has been completely isolated in a fibrous and

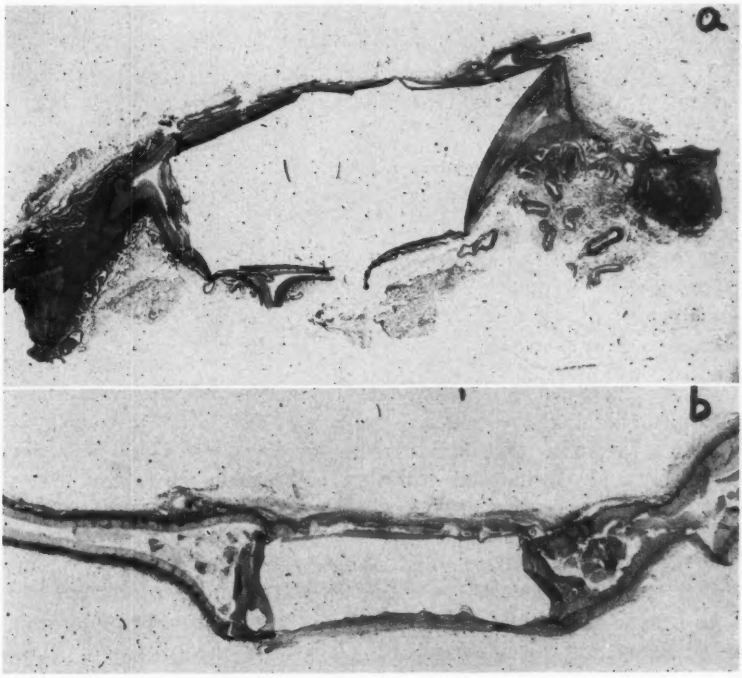

Fig. 2.—Dog 487. Longitudinal section of left lower lobe pulmonary artery (*a*) and left common iliac artery (*b*) 18 months after embolization of lead foreign body. Both vessels show foreign body in vessel completely surrounded by a "cocoon" of dense connective tissue. Adjacent to this the obstructed portions of the vessel have become endothelized.

endothelized cocoon. The blood supply to the leg was excellent and organized clot was seen for a distance of 1 cm. to 1.5 cm. on the proximal and distal sides of the "encysted" foreign body.

Reaction of Lung to Foreign Body in a Branch Pulmonary Artery.—

A total of 53 metallic foreign bodies; 41 lead bullets and 12 needle fragments were introduced into branch pulmonary arteries under the above

conditions, in a series of 28 dogs. With the large lead foreign bodies there was blanching of the involved lobe immediately after implantation. However, in half an hour the affected lobe became as pink as the uninvolved lobe. In 48 instances the lobe appeared to be grossly normal, whereas in five experiments gross infarcts were noted (Table III). For the most part, the lung appeared normal to external examination and inflated well. However, on microscopic examination a fairly severe pathologic change was present soon after embolization of the foreign body: extravasation of red blood cells, edema, and thickening of the alveolar walls in the pulmonary tissue distal

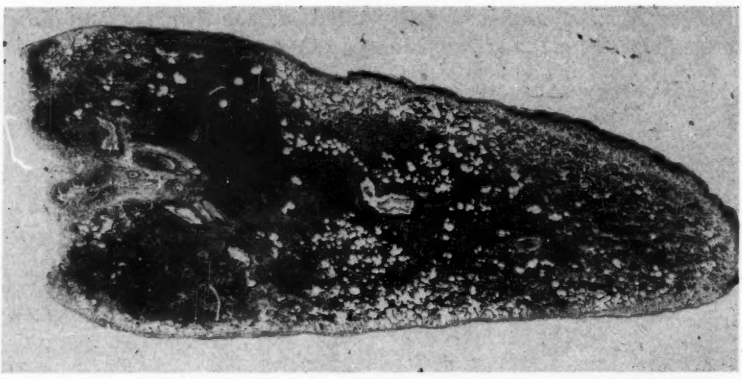

Fig. 3.—Dog 474. Peripheral section of left lower lobe of lung 2 days after embolization of lead foreign body to left lower lobe pulmonary artery. The alveoli are filled for the most part with fluid and red blood cells.

to the foreign body. Fig. 3 shows this reaction in the left lower lobe of the lung 2 days after the introduction of foreign body in the pulmonary artery of the left lower lobe. The intra-alveolar fluid and red blood cells were absorbed slowly and considerable variation was seen in the rate of absorption. There is no further improvement in the appearance of the lung noted in the period from 6 months to 2 years. Fig. 4 shows the microscopic appearance of the lung 18 months after the implantation of a foreign body in the pulmonary artery of the left lower lobe. Considerable areation of the lung has taken place as compared with the findings in Fig. 3, although perivascular and peribronchial thickening are noted.

TABLE III. PULMONARY REACTION TO FOREIGN BODY IN BRANCH PULMONARY ARTERY (53)

NO. OF DOGS	TIME	BILATERAL OPERATION	MULTIPLE F.B.	GROSS INFARCT	GROSS EDEMA	GROSS FIBROSIS	RESULT
7	1- 7 da.	3	3	2	1	0	1 died*
3	8-28 da.	1			1		Sacrificed
8	1- 3 mo.	1	3	1	1		Sacrificed
5	4- 6 mo.			1	2		Sacrificed
3	6-12 mo.	2	2				Sacrificed
3	12-24 mo.			1			Sacrificed
29		7	8	5	5	0	1

*Aspiration pneumonia.

Surprisingly little effect was seen in the roentgenogram with the foreign body in a lobar or segmental artery. However, slight infiltration was noted without gross lobar density or infiltration. Fig. 5 demonstrates a foreign body in a lobar pulmonary artery 1 month after implantation without gross evidence of pulmonary reaction in the chest roentgenogram. In Fig. 6, the lateral roentgenogram taken 18 months after the implantation of a foreign body in the left lower lobe artery shows minimal peribronchial thickening.

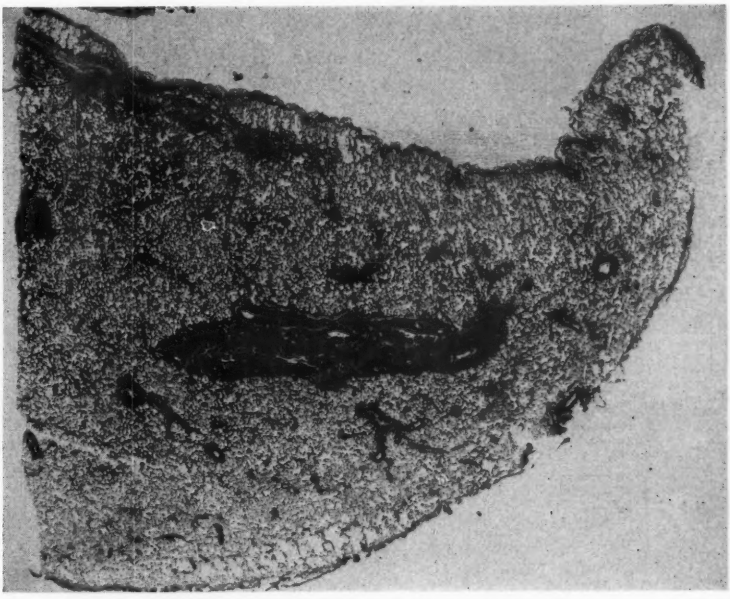

Fig. 4.—Dog 487. Peripheral section of left lower lobe of lung 18 months after embolization of lead foreign body to left lower lobe pulmonary artery. Pulmonary tissue well aerated. Perivascular and peribronchial thickening is present.

Reaction of Lung to Foreign Body in Main Pulmonary Artery.—

Experience with a foreign body occluding the main pulmonary artery was accumulated with some difficulty because even large foreign bodies tend to migrate to the branch pulmonary artery. We believe that it is true clinically that most foreign bodies entering the pulmonary circuit will migrate to a branch artery. It is logical that foreign bodies that do not occlude the lumen of the main pulmonary artery will be propelled distally by the current of blood and arterial pulsation to a point where the artery is blocked. In all of the foreign bodies involving the pulmonary artery in the experiments of Fritz and his colleagues,[6] the foreign body was lodged in a branch pulmonary artery. However, in the authors' experiments there were 8 dogs in which a large foreign body was retained in the main pulmonary artery (Table IV).

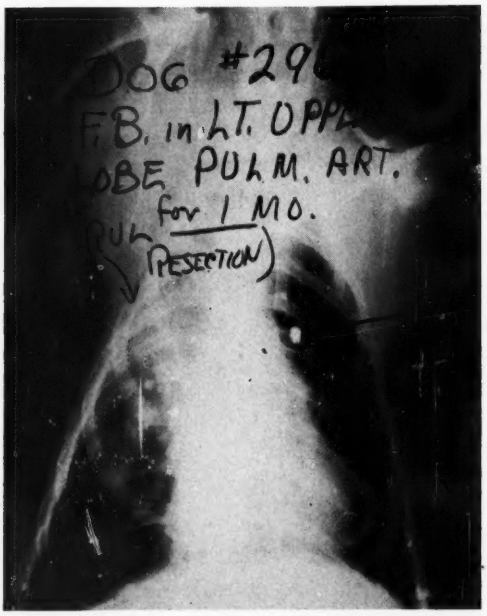

Fig. 5.—Dog 296. Roentgenogram of chest made 1 month after lead foreign body had been embolized to left upper lobe. Right upper lobe had also been resected. Lung field distal to foreign body appears normal.

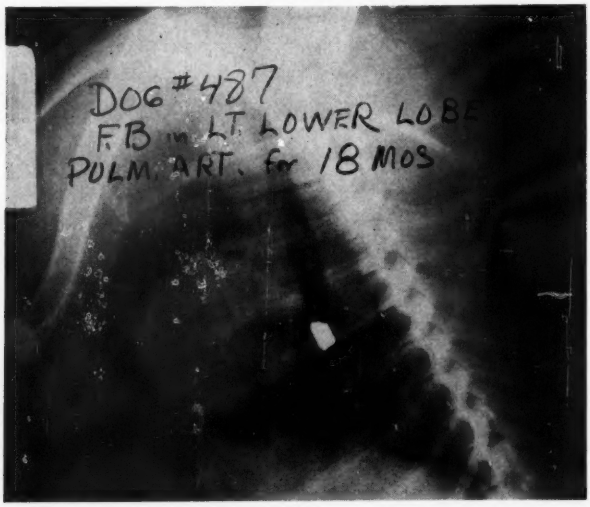

Fig. 6.—Dog 487. Roentgenogram of chest made 18 months after lead foreign body embolized to left lower lobe pulmonary artery. Lateral view shows slight peribronchial thickening.

TABLE IV. PULMONARY REACTION TO FOREIGN BODY IN MAIN PULMONARY ARTERY

DOG	DAYS	GROSS INFARCT	GROSS EDEMA	GROSS THROMBOSIS	RESULT
300	1	yes	yes	no	Died; anesthetic reaction
453	1	yes	yes	no	Died; auricular fibrillation
312	1	yes	yes	no	Died; cardiac manipulation
472	4	yes	yes	no	Sacrificed
468	10	yes	yes	no	Sacrificed
455	24	yes	yes	no	Died; bilateral foreign bodies; hypoxia
482	55	yes	yes	no	Sacrificed
342	13 mo.	yes	yes	no	Sacrificed

The entire lumen of the artery was blocked and marked changes in the lung were noted. The reaction of the lung was immediate and severe in all of the 8 animals. The lung was engorged, edematous, appearing grossly to be infarcted. Later fibrosis and organization of the lung and some areation had taken place. These observations paralleled the previously reported experi-

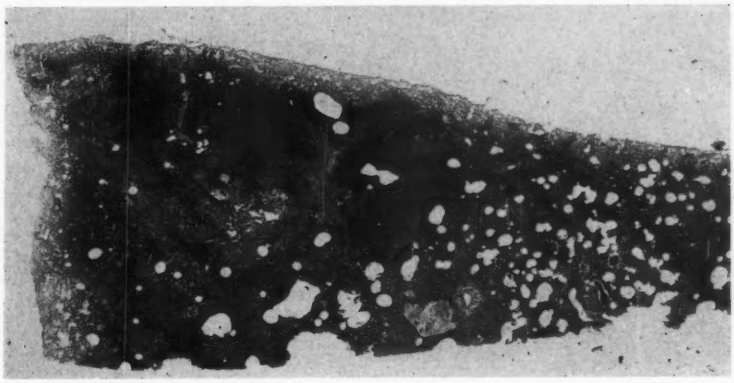

Fig. 7.—Dog 472. Peripheral section of left lower lobe of lung 4 days after embolization of lead foreign body fragment to left main pulmonary artery which was completely blocked. The lung is practically airless. The alveoli are completely filled with fluid and red blood cells.

ments in which the main pulmonary artery had been ligated.[11, 13] Even though the bronchial artery will keep the lung alive, the anatomic changes come on rapidly and are much more marked with the main pulmonary artery obstructed, than when a branch pulmonary artery is blocked. Fig. 7 demonstrates the severity of the pulmonary reaction on a low-power section of distal pulmonary tissue 4 days after the implantation of a foreign body in the main pulmonary artery. This reaction was slow to subside after the impingement of the foreign body. The roentgen findings were dramatic and showed evidence of the marked pathologic changes that were taking place in the lung, deprived of its pulmonary artery blood supply. In 1 month's time, the chest roentgenogram shows a dense shadow occupying the major part of the affected lung (Fig. 8). In 20 months, very little increased areation has taken place on the chest roentgenogram, shown in Fig. 9. This reflects the pathologic changes in the lung in which considerable fibrosis has taken place with

thickening of the interalveolar partitions which in some places present an almost solid airless lung. Thus, although the lung remains viable it is obviously damaged and appears to have little if any function. One of the females delivered multiple litters of puppies and 1 dog escaped from his cage and fought and killed another dog the day after the implantation of the foreign body. Yet in spite of the marked reaction to the foreign bodies in the main pulmonary artery, practically all of the dogs tolerated them very well.

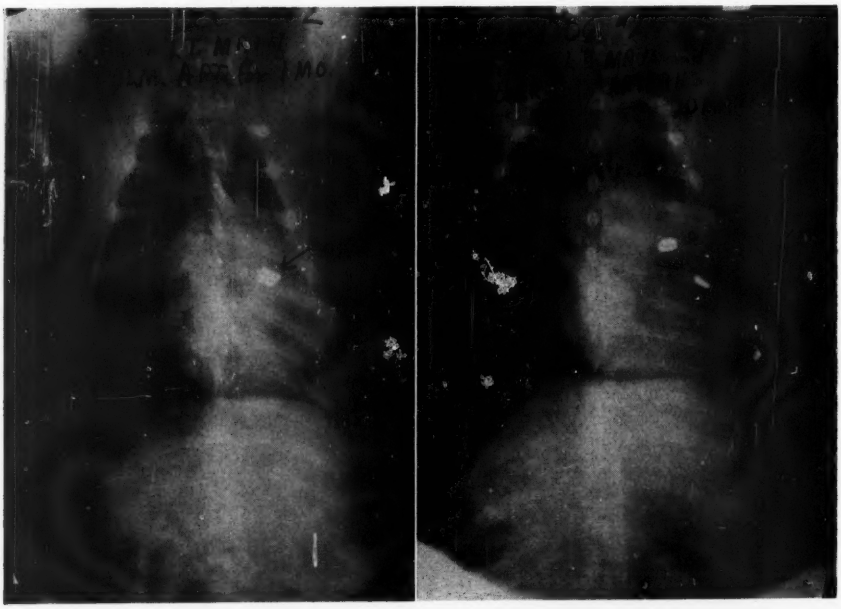

Fig. 8. Fig. 9.

Fig. 8.—Dog 482. Roentgenogram of chest made 1 month after lead foreign body embolized to left main pulmonary artery. Left lung almost completely opaque, reflecting severe pulmonary infarction.

Fig. 9.—Dog 298. Roentgenogram made 20 months after embolization of lead foreign bodies to left main and lower lobe pulmonary arteries. Some aeration of base of lung and slight aeration at apex. Remainder of lung opaque.

Role of the Bronchial Artery.—

It has been long known that the bronchial arteries play an important part in the blood supply of the lung. In some congenital cardiac anomalies accompanied by severe pulmonary stenosis or absence of the pulmonary artery, the entire blood supply may come from the bronchial arteries. Considerable experimental work has been done on the importance of the bronchial blood supply to the lung.[3, 12, 13] In all the dogs in which foreign bodies were introduced into the pulmonary arterial circulation, the bronchial arteries were engorged and dilated (markedly so in some instances).

The role of the bronchial arteries was studied in a series of 5 dogs in which the bronchial arteries of the main bronchi were divided at the time a

foreign body was introduced into a branch pulmonary artery. Reaction of the lobes to this double impairment of the blood supply was seen in severe pulmonary infarction, edema, and extravasation of blood cells. This came on early and was slow to resolve. In the animals with foreign bodies in the lobar pulmonary artery, the reaction of the lung was similar to that seen when foreign bodies lodged in the main pulmonary artery. This difference is shown in Fig. 10, *a* and *b*. Fig. 10, *a* (Dog 370) shows the effect of the foreign body placed 11 months previously in the left lower lobe branch of the pulmonary artery. The lung is well areated and the architecture is preserved. Fig. 10, *b* shows the reaction to the foreign body placed in the opposite lower lobe pulmonary artery of this same animal in which the bronchial arteries had been ligated at the time of the introduction of the foreign body. It is noted in Fig. 10, *b* that the microscopic pathologic changes are much more severe than in the lower lobe on the opposite side. In these cases the lung did not become completely gangrenous, indicating that either the intramural branches of the bronchial arteries provided some blood supply or that communicating channels existing between the lobes were sufficient to maintain the life of the lung tissue distal to the foreign body and the ligation of the bronchial artery. Intrapleural adhesions of a vascular type were not noted, so blood supply from this source seems unlikely.

The injection of a suspension of fine particulate carbon (lampblack) into the aorta just prior to the sacrifice of the animals was of considerable interest. Carbon could be readily identified in the lung distal to the foreign body, whether the main pulmonary artery or the branch pulmonary artery had a foreign body. The carbon was seen in branch bronchial arteries and appeared to reach the pulmonary tissue via bronchial pulmonary arterial communications. Fig. 11 shows diffuse pulmonary capillary embolization with the carbon particles in the lower lobe of the lung in which a foreign body had been placed in the main pulmonary artery 13 months previously. The severe pulmonary reaction of the lung distal to the foreign body in the main pulmonary artery consists of alveolar septal thickening, peribronchial and perivascular fibrosis in the partially aerated lung. These are the typical final pathologic changes seen in the lung 6 to 24 months after a foreign body occludes a main pulmonary artery. However, since the pulmonary capillaries are diffusely embolized with particulate carbon, it appears that bronchial pulmonary arterial communications are fairly extensive. They are a potent source of blood to the lung tissue distal to a foreign body in the pulmonary artery. Bloomer and associates[3] have shown that it is possible for the lung to maintain some respiratory function through the bronchial blood supply after pulmonary artery ligation.

Effect of Systemic Pulmonary Artery Anastomosis.—

The pulmonary arterial pressure is low, being from one sixth to one third that of the systemic circulation. The question arose, if a systemic artery were anastomosed to the main pulmonary artery proximal to the foreign body, would the lung be better nourished with this increased circulation from the

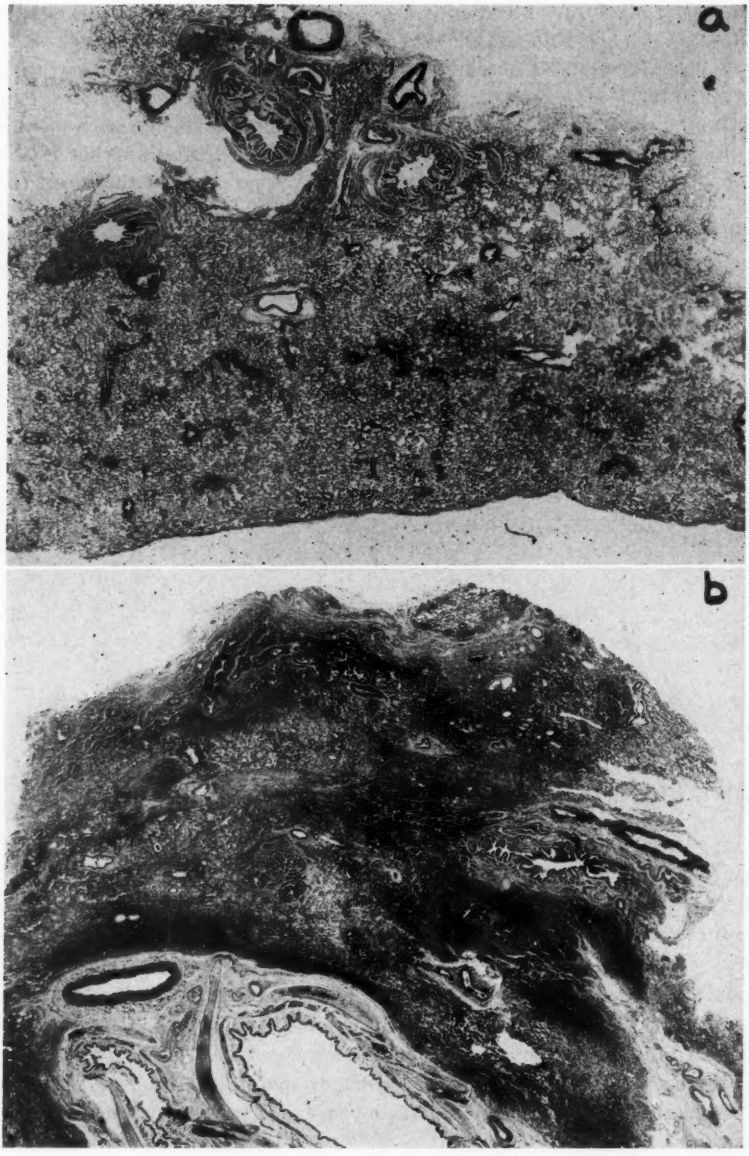

Fig. 10.—Dog 370. *a*, Peripheral section of left lower lobe of lung 11 months after impingement of lead foreign body in left lower lobe artery. Lung is well aerated and architecture preserved.

b, Peripheral section of right lower lobe of lung 11 months after impingement of lead foreign body and division of bronchial arteries. Marked interalveolar, perivascular, and peribronchial infiltration and fibrosis is noted. Lung tissue is practically airless. Reaction similar to that caused by main pulmonary artery embolization.

Fig. 11.—Dog 342. Peripheral section of right lower lobe of lung 13 months after embolization of lead foreign body in right main pulmonary artery. Fine carbon pigment injected into aorta is seen in bronchial arteries and diffusely filling pulmonary capillaries. Considerable aeration of lung has taken place but interalveolar thickening and perivascular and peribronchial thickening are present.

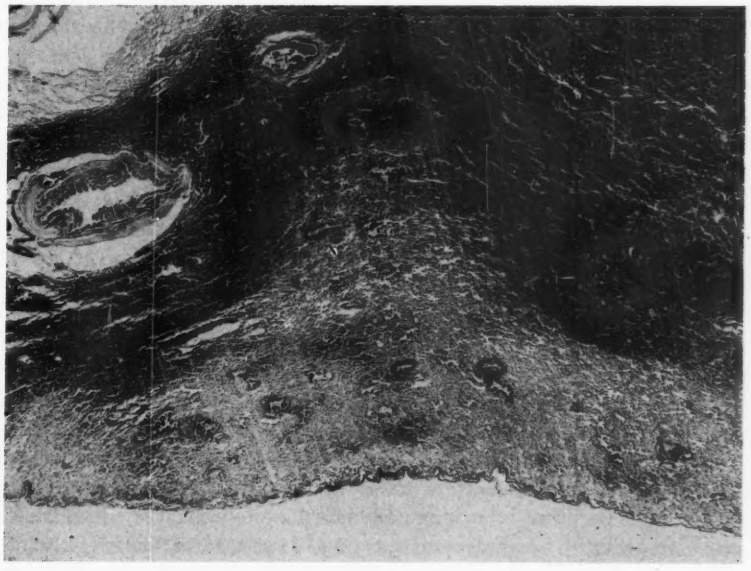

Fig. 12.—Dog 369. Section of left lower lobe of lung distal to lead foreign body embo-ized to left lower lobe 4 months previously. Anastomosis of subclavian artery to pulmonary rtery has resulted in a flooding of the lung with blood. Fibrosis and lack of aeration is oted 4 months later.

systemic arterial anastomosis? In four instances, the left subclavian artery was anastomosed to the pulmonary artery. Marked engorgement of the entire lung occurred with severe congestive changes and hemorrhage into the alveoli. The effect of the increased pressure and blood flow in the pulmonary circulation was striking, and the engorgement and hemorrhage into the lung were the same above as below the level of the foreign body in the pulmonary artery, indicating a marked flooding of the lung through pulmonary arterial capillary anastomoses (Fig. 12). In fact, similar and almost severe changes were noted in the opposite lung. Thus, it is apparent that the severe engorgement and hemorrhage in the lungs caused by the high pressure and blood flow from a systemic artery precluded the use of such an anastomosis as a means to increase the pulmonary alveolar flow to the lung distal to the foreign body.

SUMMARY

In 42 dogs in which 80 foreign bodies were introduced into the superior vena cava, pulmonary artery, or common iliac arteries, there was only one death due to the introduction of the foreign body in a long-time study covering periods up to 2 years. This death occurred in a dog who had a foreign body in the left main pulmonary artery and the right main pulmonary artery, together with a right upper lobe lobectomy. Asphyxia was apparently the cause of the death.[7]

These metallic foreign bodies were well tolerated and no erosion, hemorrhage, or secondary infection occurred and the foreign body was rapidly covered with an endothelized cocoon. Proximal or distal clotting in the pulmonary artery was not noted. A similar reaction was seen in all 14 experiments following the introduction of metallic foreign bodies in the common iliac arteries of dogs in which an excellent collateral blood supply was present.

The lung distal to a foreign body in the lobar or segmental pulmonary artery was grossly aerated and showed some gross infarction in only 5 of the 51 foreign bodies introduced into a lobar artery. The lung appeared grossly normal in all but five instances and roentgenograms were clear or showed minor changes. However, on microscopic examination of the lung, congestion, hemorrhage, and thickening of the alveoli with edema were noted soon after the embolization of the foreign body. In a period of from 6 months to 2 years, these changes gradually cleared microscopically although slight peribronchial and perivascular fibrosis persisted.

On the other hand, foreign bodies in the main pulmonary artery produced severe congestion, hemorrhage, and edema of the entire lung which appeared to be grossly infarcted. X-ray studies showed diffuse consolidation of the lung persisting for months after the blocking of the main pulmonary artery. In 2 years' time, the lungs never completely cleared although there was some aeration of the lung and the lung decreased in size. Considerable fibrosis was present. There could be little if any pulmonary function of the distal lung with the pulmonary artery (either main or branch) blocked by a

foreign body. Davis and co-workers[4] have shown that the main pulmonary artery may be occluded for periods up to 48 hours and the pulmonary changes will be reversed by re-establishment of the pulmonary circulation. After this period of time, irreversibility of change was the rule.

Bronchial arteries have an important role in supplying blood to the lung distal to a foreign body in the pulmonary circulation. Much more reaction of the lobe with bronchial artery divided was noted as compared with the bronchial artery intact. Fine carbon suspensions injected into the aorta may be seen diffusely filling the bronchial and pulmonary capillaries distal to a foreign body in the pulmonary arterial circuit. Anastomosis of a systemic vessel (the subclavian artery) to the pulmonary artery embolized by a foreign body does not prevent pathologic changes in the lung distal to the foreign body. In fact, the pulmonary engorgement, hemorrhage, and edema were so severe as to contraindicate this procedure.

CONCLUSIONS

1. In the introduction of 61 foreign bodies to the pulmonary circulation, in no case was there hemorrhage, erosion of the vessel wall, secondary infection caused by the foreign body. The foreign bodies were rapidly covered by a fibrous endothelial "cocoon" which virtually isolated them from the circulation.

2. The asymptomatic foreign body which obstructs the main pulmonary artery causes severe changes in the lung and should be removed promptly, preferably within 48 hours after embolization if pulmonary function is to be significantly restored.

3. Asymptomatic foreign body in a branch pulmonary artery produces much less general reaction of the lung than the main pulmonary arterial obstruction. However, moderately severe microscopic changes were noted coming on immediately which tend to clear after a period of months, showing a relatively clear lung on x-ray examination but with microscopic changes showing slight perivascular and peribronchial thickening and fibrosis.

4. The first 2 weeks appear to be the most hazardous for uninfected sharp foreign bodies in pulmonary arteries. After this time, there is little fear of erosion.

5. Asymptomatic foreign bodies do not need to be removed from a branch pulmonary artery for fear of erosion once encystment has taken place. However, these foreign bodies may be removed to improve pulmonary function if the vessel is large enough to anastomose or graft without subsequent thrombosis in this low pressure system.

6. Lobectomy or segmentectomy is contraindicated for these lobes are viable and, since they are well aerated, are excellent pleural space fillers, preventing overexpansion of adjacent lobes.

7. The bronchial arteries have an important role in supplying blood to the lung distal to the foreign body. Infarction in human beings may be due to differences in integrity of bronchial arteries.

8. Anastomosis of a systemic artery to a pulmonary artery containing a foreign body causes so much pulmonary congestion, hemorrhage, and edema as to contraindicate this procedure.

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(For Discussion, see page 703.)

CAUSE OF DEATH IN CARDIOANGIOGRAPHY

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THE INTRAVENOUS administration of radiopaque agents is used clinically to delineate either the urinary tract or the heart and great vessels. Whereas the mortality of intravenous pyelography is reported[1] to be less than 1:150,000, that associated with cardioangiography is ten thousand times greater, or an appreciable 2 to 5 per cent.[2] This difference has been assumed to be a reflection of the greater risk associated with the patient having cardiac disease, coupled with the fact that x-ray visualization of the heart requires an increased rate of injection as well as the use of a more concentrated organic iodide preparation. The purpose of the present investigation was to determine the mechanism responsible for these fatalities.

METHODS

General.—All experiments were carried out in adult mongrel dogs weighing between 10 and 20 Kg. The animals were anesthetized with pentobarbital sodium, 30 mg. per kilogram, supplemented with small doses of succinylcholine. Artificial respiration was provided with a positive pressure ventilator connected to a tracheal cannula. Intravascular pressures were measured with Statham transducers and recorded on a Sanborn Poly-Viso recorder. Heparin (2 mg. per kilogram) was administered for anticoagulation. Donor blood used in the perfusion experiments was collected into plastic beakers containing enough heparin to produce a final concentration of 5 mg. per 100 ml. of blood.

Open Chest Animals.—The chest was opened through the left fifth interspace. Polyethylene catheters were placed in (a) the main pulmonary artery, (b) the left atrium, (c) the aorta through the femoral artery, and (d) the inferior vena cava from the femoral vein. Injections were made rapidly through a No. 10 Fr. catheter placed into the vena cava through either the femoral or jugular veins. The majority of the solutions administered consisted, because of their current favor, of commercially available 50 to 90 per cent diatrizoate salts of sodium and methylglucamine (Hypaque and Renografin). The remaining studies were carried out using 80 per cent NaI, 70

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to 75 per cent preparations of iodopyracet (Diodrast), iodomethamate (Neoiopax) and acetrizoate (Urokon), and finally 40 per cent methiodal sodium (Skiodan). Isotonic saline and dilute solutions (30 to 35 per cent) of the various radiopaque agents were used as controls.

Isolated Perfused Lung.—The chest of the animal from which the lung was to be obtained was opened under artificial respiration by splitting the sternum longitudinally. The azygos vein and vena cava were ligated after heparinization and the heart, lungs, and aorta were removed without interrupting ventilation. The plastic cannula which had been filled to its tip with perfusion fluid was inserted through the outflow tract of the right ventricle and tied into the main pulmonary artery. Care was taken to keep air out of the pulmonary circulation. The pericardium, both ventricles, and the right atrium were dissected off and the left atrium drained at near zero pressure. The lung was suspended in a perforated plastic plate and venous drainage was collected in a plastic funnel and recirculated with a Sigmamotor pump. Perfusion was begun after an interruption of less than 2 minutes. The perfusion rate remained constant and was determined by increasing the arterial pump to the highest flow consistent with normal pulmonary arterial pressures monitored through a needle-tip catheter. Oxygenation was maintained by ventilating the lung throughout the experiments. Injections were made proximal to the arterial pump. Perfusates consisted of either whole blood, red cell mixtures, plasma, serum, or dextran-Ringer's solution. If blood was not to be used initially the lung was first flushed with large volumes of saline and dextran. Thoroughness of the rinsing was gauged by the whiteness of the lung surface and the clarity of the solution emerging from the venous drainage.

Total Body Perfusion.—Total body perfusion was carried out by previously described techniques.[3] The blood pressure response to radiopaque agents was determined under conditions of constant flow to quantitate the change in total peripheral resistance.

RESULTS

Intact Animal.—A total of 44 injections was made in 16 dogs. Respiratory alterations were prominent but will not be considered further at this time. The vascular response to these agents was variable. Marked reactions occurred either with heavier animals in which the absolute volume administered was greater, or when osmotically more concentrated materials were used regardless of chemical identity. A striking bradycardia with evidence of intracardiac block was frequently noted. Pulmonary edema, arterial desaturation, and signs of congestive failure appeared after repeated injections. The blood pressure always fell in response to these agents. Three distinctive patterns of decline, essentially unaffected by vagotomy, could be elicited in spite of some overlap.

1. *Monophasic hypotension with or without death of the animal:* The animals died in half of the 16 instances when 1 ml. per kilogram of sodium iodide,

iodomethamate, or methiodal sodium was injected (Fig. 1). A similar result was obtained in 4 out of 6 cases with 3 ml. per kilogram dosages of 90 per cent diatrizoates (Fig. 2). Characteristically, as shown in Figs. 1 and 2, the blood pressure fell precipitously and never recovered, pulmonary artery pressure increased strikingly while left atrial pressure fell, central venous pressure rose with vigorous pulsations, and the heart continued to beat for some time. Inspections showed the left ventricle to be collapsed. A similar response with eventual recovery was seen in the remaining studies with sodium iodide, iodomethamate, methiodal sodium, and high dosages of diatrizoates.

2. *Diphasic hypotensive response:* This type of reaction occurred frequently after injection of 1 ml. per kilogram of 90 per cent diatrizoate (12 of 18), 70 per cent acetrizoate (3 of 5), and 75 per cent iodopyracet (3 of 4) (Fig. 3). A milder variant was encountered with a similar dosage of 70 per cent diatrizoate (2 of 7). Initially there was a decline in blood pressure identical to that described above, with bradycardia, occasional missed beats, and a decrease in pulse pressure. However, the arterial pressure rapidly recovered, with resolution of the pulmonary hypertension and an overshoot in left atrial pressure. A more prolonged hypotension then ensued, with tachycardia, increased pulse pressure, and a loss of the dicrotic notch in the pressure tracing. A concurrent secondary rise and fall in pulmonary arterial and vena caval pressures were also noted. It should be pointed out that the early pulmonary hypertension was frequently accompanied by similar changes in the pulmonary vein despite normal left atrial readings.

3. *Paradoxical reaction:* The remainder of the 1 ml. per kilogram injections of radiopaque agents, including all solutions examined with 50 per cent or lesser concentrations, showed a paradoxical response (Fig. 4) in that the typical delayed systemic hypotension was preceded by a hypertensive phase. Initial pulmonary hypertension was never seen. Sometimes in the early period a dip in blood pressure occurred that resembled the diphasic reaction in the presence of bradycardia and missed beats.

Isolated Perfused Lung.—Sixteen lungs were perfused. Flow rates were below normal, varying from 44 to 110 ml. per kilogram per minute. Mean pulmonary artery pressures were physiologic, however, ranging from 5 to 25 mm. Hg, the lower figures being obtained with plasma perfusates. The degree of ventilation had no effect on the findings.

In most cases the lung was first perfused with a colloid solution; subsequently blood or various red cell suspensions were used. Radiopaque agents, including 80 per cent NaI in doses of up to 1 ml. per kilogram, never produced pulmonary hypertension in the absence of red cells in the perfusate. In fact, pulmonary vascular resistance generally fell under these conditions except when viscous diatrizoate solutions were injected. In contrast, a phasic increase in pulmonary arterial pressure was almost uniformly seen when similar amounts were introduced into circulating blood or red cell suspensions (Fig. 5). NaI, methiodal, and iodomethamate solutions gave such violent reactions that only

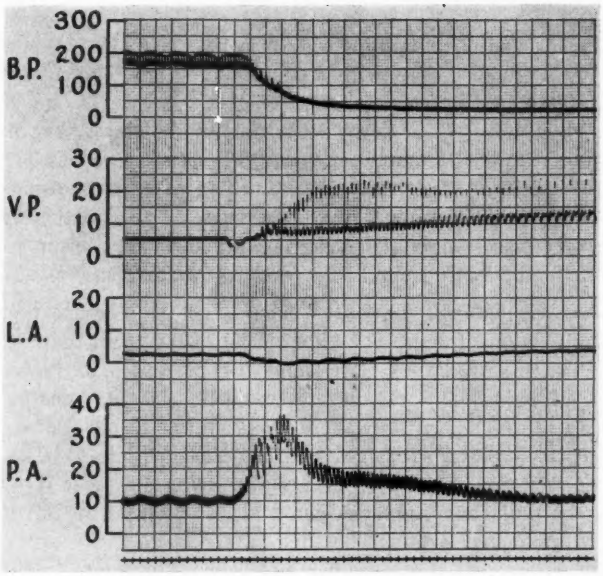

Fig. 1.—A typical monophasic hypotensive response produced in this dog by the rapid intravenous administration of 1 ml./Kg. of 75 per cent Neo-Iopax. Systemic blood pressure declines precipitously, accompanied by a rising venous pressure. Similarly, left atrial pressure falls with an associated pulmonary hypertension. These findings are consistent with death from acute cor pulmonale brought about by obstruction to blood flow through the lungs. (Time in seconds.)

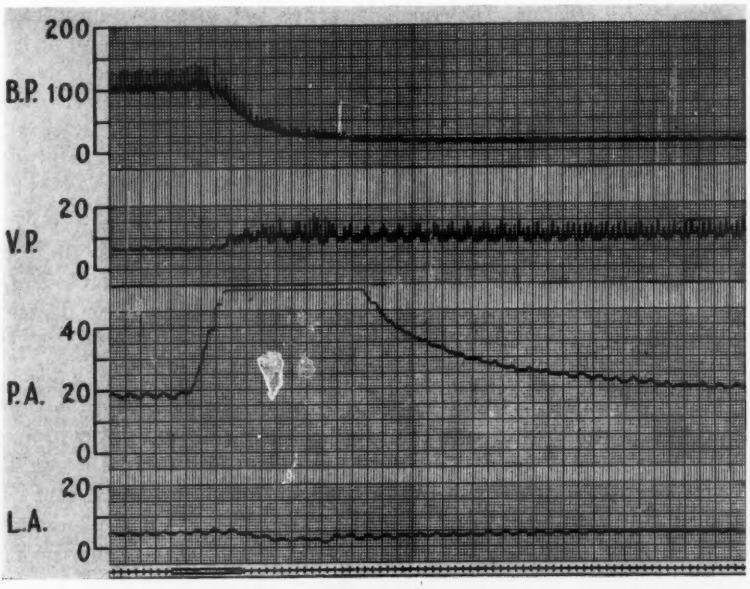

Fig. 2.—Another example of a monophasic hypotensive response seen after the intravenous injection of 3 ml./Kg. of 90 per cent Hypaque. Systemic and pulmonary pressure changes are similar to Fig. 1 and again result in death of the animal.

doses of less than 0.5 ml. per kilogram could be used without running the risk of completely obstructing blood flow through the preparation. Typically, except in the more severe reactions, the change in vascular resistance was over within 30 seconds in spite of recirculation. The 70 to 90 per cent iodopyracet,

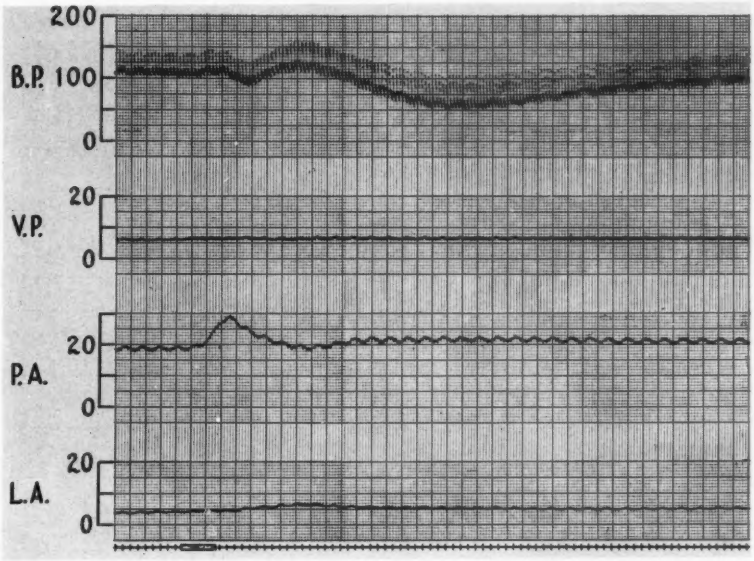

Fig. 3.—Diphasic hypotensive response produced with 1 ml./Kg. of 90 per cent Hypaque. Early hypotensive phase, seen in Figs. 1 and 2, is here foreshortened by a recovery stage with a rise in systemic and left atrial pressures. Final prolonged hypotensive phenomenon is accompanied by a shallow increase in pulmonary artery pressure.

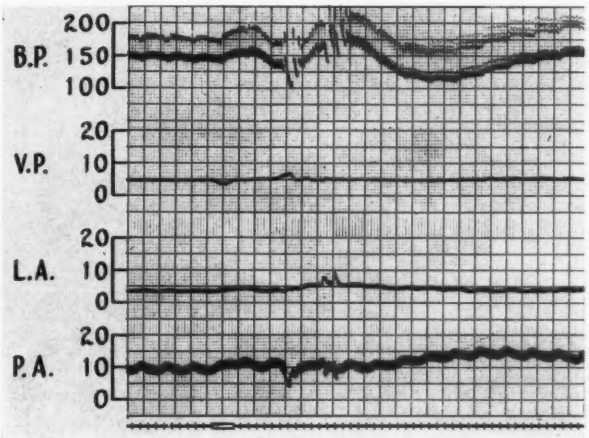

Fig. 4.—Paradoxical response obtained with 1 ml./Kg. of 50 per cent Hypaque. Initial pulmonary hypertension is absent and is replaced by a fully developed hypervolemic phase with systemic hypertension. Note the marked bradycardia shown to be a result of both vagal and direct cardiac excitation. Pulmonary artery pressure rises only with the late hypotension.

acetrizoate, and diatrizoate solutions required almost the full dosage of 1 ml. per kilogram to double pulmonary artery pressure. The degree of response was in general proportional to the osmotic activity of the preparation tested. A positive response was never seen with 30 to 35 per cent concentrations. Microscopic examination of small blood vessels in the lung during a reaction

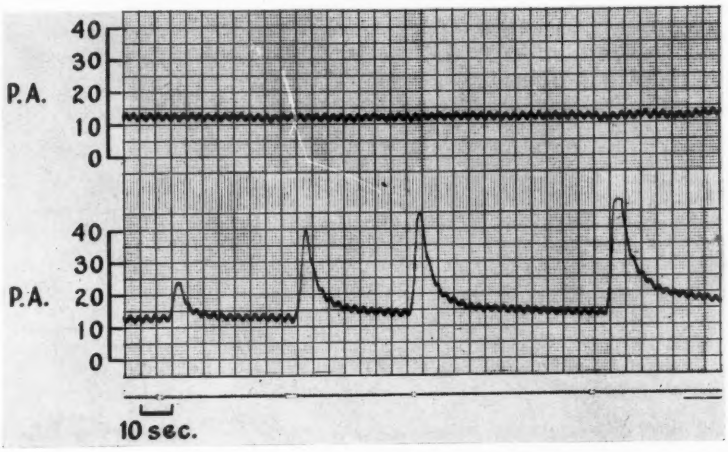

Fig. 5.—Effect of 1 ml./Kg. of 70 per cent Urokon, 90 per cent Hypaque, 70 per cent Diodrast, and 40 per cent Skiodan, respectively, on pulmonary artery pressure in the isolated lung perfused at a constant flow, first with plasma and then blood (below). The phasic increase in pulmonary vascular resistance is completely dependent upon the presence of red cells in the perfusate and is transitory in spite of recirculation.

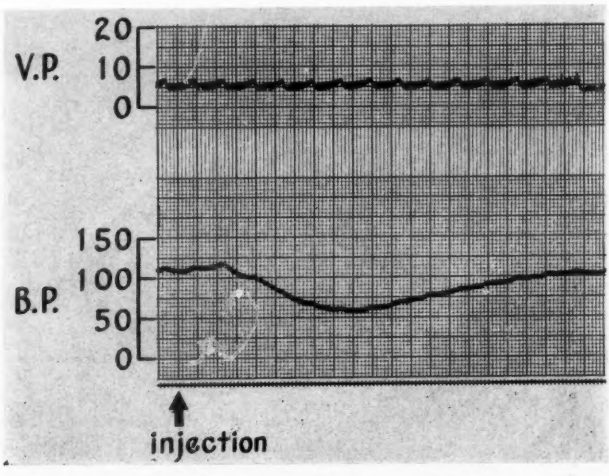

Fig. 6.—Effect of the intra-arterial administration of 1 ml./Kg. of 90 per cent Hypaque in the totally perfused dog. Note fall in arterial pressure at constant flow without change in venous pressure indicating an over-all decline in peripheral resistance. The flow in the aorta under these conditions is turbulent and red cell agglutination does not play as significant a role as seen after intravenous injection (Fig. 3).

showed red cell agglutination, plugging of arterioles and venules, and plasma skimming. Vasoconstriction was never observed. Instead, an average increase of about 20 per cent in vascular diameters occurred with re-establishment of blood flow. Permanent sections showed vascular congestion, pulmonary edema, red cell sickling, diapedesis, and clumping. A similar appearance has previously been reported in the intact animal.[4] The experiments were terminated after multiple reactions had been obtained because of the development of massive pulmonary edema.

Total Body Perfusion.—All of the agents used, ranging from 30 to 90 per cent in concentration, produced a fall in blood pressure at constant flow (Fig. 6). No effect was seen with isotonic saline. Various injections were made in 8 experiments.

COMMENT

Dotter and Steinberg[5] reported in 1949 that cardioangiography had been performed in over a thousand cases without fatality. They (and others)[6, 7] believed that this procedure was both simple and safe, giving rise only to a sensation of warmth with occasional mild respiratory symptoms. Recently, perhaps because of more liberal dosages, disturbing side effects have been reported. These have included vascular collapse,[8] electrocardiographic abnormalities,[9-11] pulmonary edema,[12] cyanosis,[13] and death.[14] Increasing awareness of this hazard has to a certain extent dampened the original enthusiasm for the procedure.

Vasomotor reactions to radiopaque agents have been recognized for some time in the experimental animal. Between 1933 and 1935, five different groups[15-19] of investigators demonstrated the hypotensive potentialities of these solutions and suggested that both central and peripheral actions were involved. Weatherall,[20] in 1942, considered vasodilatation to be the primary mechanism. However, Gordon and his associates,[21] in 1950, described a "Diodrast reaction" in the dog which included bradycardia, cardiac irregularities, and a rise in central venous pressure. These findings have been confirmed by other workers.[22, 23] Rowe and associates,[24] in 1956, were the first to mention the occurrence of pulmonary hypertension. They observed this response in both the experimental animal and a patient who later died.

The present study demonstrates unequivocally that radiopaque preparations lower peripheral resistance. This finding, combined with the previously described pulse pressure, pulse wave, plethysmographic, skin temperature, and microscopic changes,[25] confirms the vasodilatory nature of these compounds shared with other hypertonic solutions.[26] This effect is delayed after intravenous injection because it depends upon direct contact with the peripheral vasculature. The elevation in pulmonary artery pressure, venous pressure, and heart rate seen at this time suggests a compensatory adrenergic release. This relatively benign peripheral phenomenon, perhaps of importance only in hypertensive and arteriosclerotic disease, is preceded by the possibility of a potentially much more dangerous reaction—obstruction to blood flow through the lungs.

Pressure data in Figs. 1 and 2 indicate that all of the dogs who succumbed did so of acute cor pulmonale. Circumstantial evidence obtained from case reports on patients who died suggests a similar cause of death, the respiratory system being vulnerable.[27] Almost all of the fatalities were in individuals known to be suffering from some type of central or peripheral pulmonary vascular stenosis.[28] Cyanosis, dyspnea, and signs of pulmonary congestion were noticeable at death. Pulmonary infarction, edema, and hemorrhage were prominent autopsy findings.

These experiments also provide information regarding the mechanism responsible for the increase in pulmonary vascular resistance. The studies in the whole animal show that the site of obstruction to blood flow through the lungs may be proximal or distal to the capillary bed. This phenomenon persists in the isolated preparation demonstrating that the central nervous system is unnecessary for its development. Its transitory nature in spite of recirculation is against an indirect effect mediated through the release of vasoactive materials. However, a direct action on the pulmonary vasculature is also ruled out because no response is elicited when red cells are absent from the perfusate. To be consistent with these observations any theory regarding the pulmonary vascular effects would have to assume that radiopaque agents increase the viscosity of the blood passing through the lungs by affecting its red cell component. The hypothesis is confirmed by the microscopic demonstration of red cell agglutination with plugging of vascular channels throughout the pulmonary parenchyma. This potential for altering the stability of the red cell stream is shared with other concentrated salt[29] and sugar solutions but not by urea which is unable to exert an osmotic differential across the red cell membrane.

On the basis of unpublished observations,[30] it appears that markedly hypertonic solutions, when given intravenously, immediately penetrate the red cells. These hypertonic erythrocytes become damaged and hemolyzed after passage through the circulation when they are re-exposed to a normal environment. Red cell agglutination is the first stage of this paradoxical hypotonic hemolysis.[31] The present studies show that doses up to 1 ml. per kilogram give rise to detectable changes in blood viscosity only when the osmotic activity of the solution is greater than 1,500 mOsm. per liter. Larger volumes tend to lower this threshold. The central effect requires a much stronger solution than the vasodilatation seen in the peripheral vasculature. This is well demonstrated by the paradoxical response elicited by relatively dilute radiopaque agents. Here, pulmonary hypertension is absent allowing the previously masked effects of hypervolemia and Bezold or direct cardiac excitation to develop before the later systemic hypotension.

A number of investigators have noted an association between the osmotic activity of angiographic media and their toxicity.[17, 20, 23, 24] Cotrim,[32] in 1955, clearly demonstrated this relationship but, in the absence of pulmonary vascular measurements, attributed death to primary cardiac depression. Most toxicity studies have been performed in small animals using relatively slow rates of injection. The lethal dose under these conditions is 4 or 5 times greater

TABLE I. OSMOTIC CONCENTRATION OF RADIOPAQUE PREPARATIONS

SOLUTION	OSMOTIC ACTIVITY (mOsm./L.)	RATIO TO PLASMA (330 mOsm./L.)
30% Urokon	950	3
35% Diodrast	1,100	3-4
50% Miokon	1,395	4-5
50% Hypaque	1,490	4-5
76% Renografin	1,730	5-6
70% Urokon	2,300	7-8
70% Diodrast	2,320	7-8
90% Hypaque	2,330	7-8
40% Skiodan	3,100	9-10
75% Neo-iopax	4,100	12-13

than that described at this time and chemical constituency appears to be more important.[33] Anaphylaxis continues to be mentioned as the cause of death in cardioangiography despite the fact that preliminary negative sensitivity tests are the rule.[34]

The phenomenon of red cell agglutination explains a number of hitherto poorly understood clinical observations. Complications have increased sixfold since 35 per cent solutions (originally developed for intravenous urography) have been replaced by 70 per cent preparations.[35] The newer less toxic radiopaque agents tend to have a lower osmotic activity because of their larger molecular size, poorer dissociation, and the replacement of inorganic by organic cations. The group of patients in which cardioangiography is known to have the greatest risk is that exemplified by the Eisenmenger syndrome. Here red cell agglutination is accentuated by polycythemia while the already damaged lungs are obviously more susceptible to vascular blockage. An increase in pulmonary vascular resistance is especially dangerous in this situation because systemic resistance is simultaneously lowered by the peripheral vasodilatory effects and the two circulations are connected by a right-to-left shunt.

In conclusion, it should be pointed out that the risk of agglutination could be markedly reduced, if not eliminated, by changes in the characteristics of the more concentrated radiopaque preparations. An attempt should be made to limit their osmotic activity to less than 1,500 mOsm. per liter by either decreasing their solubility or increasing their molecular size. A more difficult line of approach would be the development of solutions whose permeability, like urea, is so great that they are unable to develop an osmotic differential across the red cell membrane.

SUMMARY

One to 3 ml. per kilogram dosages of various concentrated radiopaque agents have been rapidly injected into the venous system of 24 dogs. A late peripheral vasodilatation was routinely observed. Solutions having an osmotic activity greater than 1,500 mOsm. per liter generally produced an initial pulmonary hypertension which sometimes resulted in death from acute cor pulmonale. Studies in the isolated perfused lung showed that the increase in

pulmonary vascular resistance was related to the presence of red cells in the perfusate. Microscopic observations demonstrated that these commercial preparations can cause red cell agglutination which is responsible for the pulmonary effects. The significance of these findings has been discussed in relation to clinical experience.

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(For Discussion, see page 703.)

PHYSIOLOGIC RESPONSE OF THE CORONARY CIRCULATION TO UNILATERAL PULMONARY ARTERY LIGATION

I. Initial Experimental Study

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A SIMPLE operative procedure capable of increasing the extracardiac collateral circulation to the coronary arteries deserves evaluation. Previous studies of the bronchial artery circulation impressed us with the increase in extracardiac collateral coronary blood flow which follows unilateral pulmonary artery ligation.[1, 2, 3]

Small extracardiac communications are normally present between the systemic circulation and the coronary arteries, but the flow through these vessels is of little significance in the normal dog. After chronic unilateral pulmonary artery ligation, these small communications become greatly dilated and are capable of carrying a large blood flow. The coronary arteries apparently contribute to the extensive collateral circulation of the lung after pulmonary artery occlusion. Under the experimental conditions outlined in this study (Fig. 1), these extracardiac collateral vessels may also carry a large volume of oxygenated blood into the coronary arteries. The purpose of this investigation is to determine the physiologic response of the isolated coronary vascular bed to a well-developed extracardiac collateral circulation. The anatomy of the extracardiac collateral coronary circulation has been accurately described for more than 50 years[4] but its physiologic significance is not generally appreciated. In recent years Gross,[5] Meek,[6] Hudson,[7] Kugel,[8] Gregg,[9, 10] Liebow,[11-14] Bloomer,[11, 12, 14] Vidone,[13] Glenn,[15] and their associates have contributed to our knowledge of this little understood but most significant collateral circulation.

A principal source of extracardiac collateral blood flow to the heart and lungs comes from the aorta through the bronchial arteries. Part of this systemic circulation is apparently shunted directly into the coronary vascular bed

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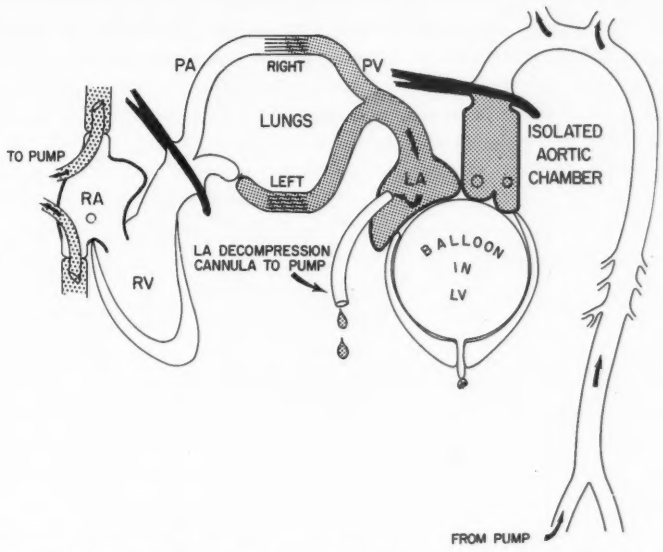

Fig. 1.—The experimental method which emphasizes the left auricular drainage, balloon occlusion of the left ventricle, and the creation of an "isolated aortic chamber."

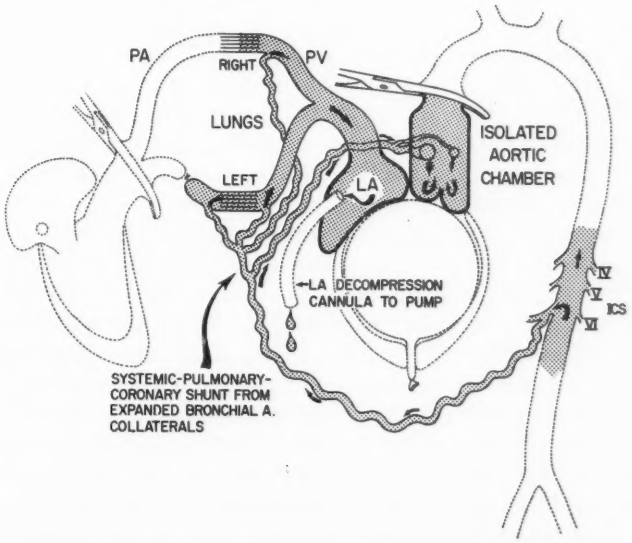

Fig. 2.—The diagrammatic representation of the aortic-pulmonary-coronary collateral flow, in the dog, which passes through the bronchial arteries.

while the remainder passes through the lungs and is returned to the left auricle (Fig. 2). In this experimental study we were able to investigate the systemic-coronary collateral circulation alone (Fig. 3). A direct measurement of the isolated extracardiac collateral blood flow to the coronary vascular bed, completely independent of the pulmonary venous-left auricular return, to our knowledge, has not been previously reported.

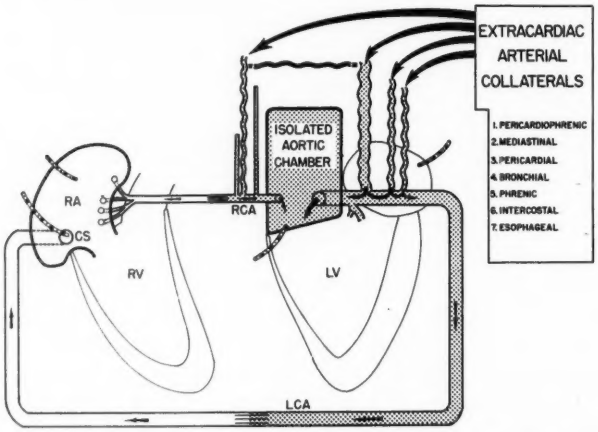

Fig. 3.—A diagram of the extracardiac sources from which arterial blood enters the isolated coronary vascular bed through auricular branches of the coronary arteries, under the conditions of the experimental method (after chronic unilateral pulmonary artery ligation). The retrograde flow into the "isolated aortic chamber" through the coronary ostia and the forward flow through the coronary vascular bed is demonstrated.

EXPERIMENTAL METHOD

Acute experiments were performed in 14 dogs (11 to 20 Kg.); 5 were control animals, and, in 9 dogs, the left pulmonary artery had been ligated from 3 to 19 months. Sodium pentobarbital anesthesia was used and a positive endotracheal pressure of 9 to 12 cm. H_2O was maintained by a mechanical respirator. Complete pump dependency was employed (disc oxygenator) and the aorta and pulmonary artery were clamped simultaneously within the pericardium. Either potassium citrate or anoxic cardiac arrest was utilized and the left auricle was immediately decompressed through a cannula which drained into the venous return to the pump. The coronary sinus, right auricle, ascending aorta (below the clamp), femoral artery and pulmonary artery were cannulated and pressures and flows recorded. The cardiac septa were intact. A balloon was inflated in the left ventricle of 10 animals (4 were controls) to prevent any remaining pulmonary venous flow from reaching the coronary ostia (Fig. 1). This created an "aortic chamber" which completely isolated the coronary ostia from all blood flow except that which came from extracardiac sources. Serial oxygen saturation determinations were made and continuous electrocardiographic tracings recorded. Repeated flows were measured from

the cardiac cannulas with a graduate and timed for 30 seconds or longer. In several instances, a cannula was introduced into the left coronary ostia directly, through an aortotomy, to record the pressure and flow. At the completion of each experiment, plastic casts and angiograms were prepared of the collateral circulation to the heart and lungs by injecting 10 per cent radiopaque vinyl plastic into the doubly clamped descending thoracic aorta, containing only the bronchial and lower intercostal arteries. Temperatures varied during these experiments between 30° and 34.5° C.

This experimental method isolated the coronaries so that the extracardiac collateral circulation alone which perfused this vascular bed could be studied. The term, "high flow," will be used to designate the animals with chronic unilateral pulmonary artery ligation.

RESULTS

The results of this investigation were consistent in both the group with pulmonary artery ligation and in the controls. Only 5 of the 9 animals with an expanded collateral coronary circulation were studied with a balloon in the left ventricle. The remaining 4 dogs, however, showed the same response as the 5 reported, except that their coronary sinus return was greater without the compression effect of the inflated balloon. The coronary sinus flow was absent in the controls with a total coronary venous return of less than 1 ml. per minute. The group of animals with pulmonary artery ligation all showed more coronary venous flow than the controls and, in some instances, these flows were very high.

Studies previously reported and observations during this investigation impressed us with four important findings in dogs with chronic pulmonary artery ligation: (1) a prolonged sinus rhythm (up to 83 minutes) following pulmonary artery and aortic occlusion with the left auricle decompressed; (2) the inability to electively arrest the heart for more than a few minutes with potassium citrate; (3) the presence of 10 per cent vinyl plastic in the left coronary artery when the injection was made only into the doubly clamped descending thoracic aorta; and (4) a persistent flow of oxygenated blood into the right heart during cardiac arrest with pulmonary artery and aortic occlusion. These findings were entirely absent in the control animals.

In Fig. 4, the large volume of coronary venous return is recorded in an animal with ligation of the left pulmonary artery for 18 months. A volume of 135 ml. per minute passed through the isolated coronary vascular bed from extracardiac sources alone; when the left auricular drain was occluded, pulmonary vascular pressure rose with an increase in flow to 180 ml. per minute. After vasopressor stimulation, the flow was 360 ml. per minute and promptly fell to 8 ml. with Arfonad administration. These pharmacologic responses reflect the intimate relationship between this extracardiac collateral coronary flow and the systemic circulation.

The mean coronary sinus flow rates, expressed in terms of square meters of body surface (approximately 60 per cent of the coronary venous return?),

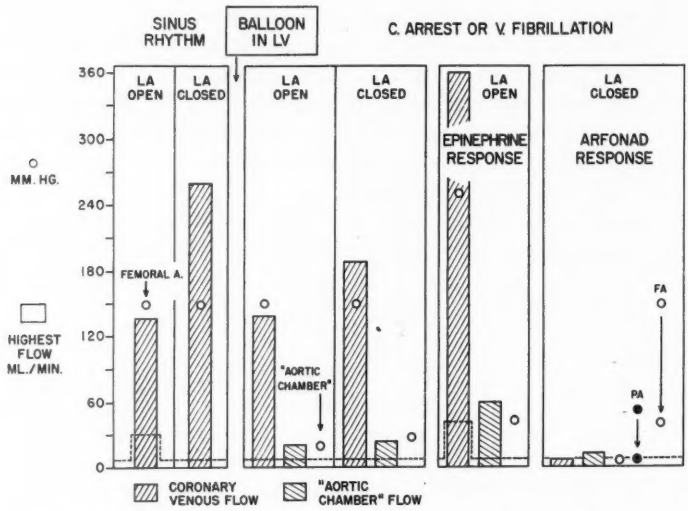

Fig. 4.—Dog 169. This graph demonstrates the high coronary venous flow which is present after prolonged unilateral pulmonary artery ligation (18 months). The pharmacologic response of the extracardiac collateral circulation to vasopressor and vasodilator drugs substantiates the systemic arterial origin of this collateral. The maximum response of the control group is represented by the broken line. Total cardiopulmonary bypass is present with aortic and pulmonary occlusion.

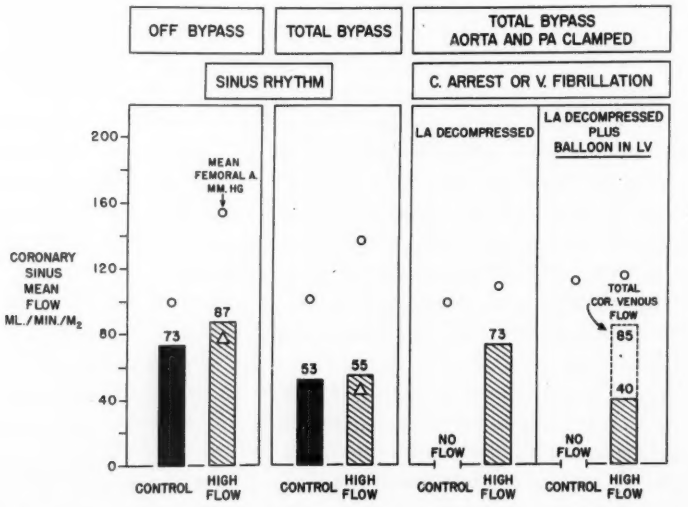

Fig. 5.—A graphic comparison of the mean coronary sinus flow (ml./min./M.²) in both groups of dogs (5 control—5 high flow dogs). The controls show *no coronary sinus flow* in the two boxes on the right, in contrast to the large flow present in the high flow group. (Δ—flow rates not recorded in 1 animal.)

in both groups of animals are compared in Fig. 5. When the coronary vascular bed was completely isolated, there was no coronary sinus flow in the control group, but the animals with a high extracardiac collateral flow showed a mean volume of 40 ml. per minute which passed through the coronary sinus. There was a fall in flow in the ligated pulmonary artery group from 73 to 40 ml. per minute after inflating the left ventricular balloon; this presumably represented an interference with coronary artery filling. However, during this fall the total mean coronary venous return was 85 ml. per minute, even though there was a complete absence of normal coronary blood flow, and represented the flow from extracardiac collateral communications into the coronary vascular bed. This extracardiac collateral flow was equal to the coronary sinus flow in the normal beating heart with the animal off the pump.

Studies of the "isolated aortic chamber" showed a pressure of 5 to 7 mm. Hg with an absence of flow in the controls. The high flow group demonstrated a mean pressure of 19 mm. Hg and a flow of 29 ml. per minute with oxygen saturations of 90 per cent (Fig. 6). There was no flow in the control group and oxygen saturations could not be determined.

The mean pulmonary venous flow into the left auricle during these experiments was 274 ml./min./M.^{2} in the high flow group and 23 ml./min./M.^{2} in the controls.

The 10 per cent radiopaque plastic did not enter the extracardiac collateral coronary circulation in the control animals but was present in the animals with pulmonary artery ligation.

DISCUSSION

This study emphasizes the marked difference between the meager extracardiac collateral coronary artery flow normally present and the very high collateral flow which results after prolonged unilateral pulmonary artery ligation, in the experimental animal. A period of 5 months or more seems to be required following pulmonary artery occlusion to establish well-developed collaterals between the systemic-coronary circulation.

Liebow, Bloomer, and their associates[14] have indirectly measured the collateral flow to the coronaries in the intact, living animal, employing dye dilution techniques, after cardiopneumopexy and pulmonary artery ligation. They concluded that the collateral blood flow entering the coronary sinus was 4 to 16 per cent[14] of the total coronary sinus flow, in the absence of myocardial ischemia, and suggested the possibility of ligating a lobar pulmonary artery in patients with "coronary insufficiency."

The dog's heart is left coronary preponderant, in contrast to the human heart; however, it is of interest that Louis Gross,[5] in his classical monograph published in 1921, described the coronary blood supply in *100 human hearts* and demonstrated a shift from a right or balanced coronary heart to left coronary preponderance during the *fourth* to the *eighth* decades of life.

The clinical application of this experimental study to human patients is speculative at this time. Further investigations are now in progress in an effort

to clarify certain physiologic aspects of this simple operative procedure, unilateral ligation of the pulmonary artery.

SUMMARY

A comparison of the results in the control animals and high flow dogs with unilateral pulmonary artery ligation is shown in Fig. 6.

		CONTROLS	HIGH FLOW
WELL EXPANDED EXTRACARDIAC CORONARY A. COLLATERALS		ABSENT	PRESENT WITHIN 5 to 12 MONTHS
CARDIAC ARREST	ANOXIC	ARREST WITHIN 15 MINUTES	SINUS RHYTHM FOR 23 to 83 MINUTES
	POTASSIUM	PROLONGED	SHORT DURATION
PLASTIC (10%) STUDIES		NO CORONARY A. FILLING	LEFT CORONARY A. FILLS
BALLOON IN L.V. — L.A. OPEN			
CORONARY VENOUS FLOW (MEAN)		0.8 ML./MIN./M_2 (NO COR. SINUS FLOW)	85 ML./MIN./M_2 (COR. SINUS FLOW-40)
"ISOLATED AORTIC CHAMBER" (MEAN)	PRESSURE	5 MM. HG	19 MM. HG
	FLOW	NO FLOW	29 ML./MIN.
	O_2 SATURATION	NO FLOW	90%
LEFT AURICULAR FLOW (MEAN)		23 ML./MIN./M_2	274 ML./MIN./M_2

Fig. 6.—A summary of the important differences in the physiologic response of the extracardiac collateral coronary circulation in the two groups of dogs.

CONCLUSIONS

Recognizing that these are experimental studies, performed in the bypassed heart under altered physiologic conditions, the results are nevertheless significant and demonstrate the potential extracardiac blood flow which is capable of entering an isolated coronary arterial bed, after the chronic ligation of one pulmonary artery. Further experimental and clinical investigation is necessary to determine the advisability of employing pulmonary artery ligation in patients with coronary artery disease.

We wish to express our appreciation to Mr. Boyd Perry, Mr. Thomas Perry, Mrs. Mary E. Garrard, and Mr. Eugene Varga for their technical assistance.

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DISCUSSION

(PAPERS BY WRIGHT [PAGE 643], HARDY [PAGE 652], BRUNS [PAGE 662], BREWER [PAGE 670], READ [PAGE 685], LITTLEFIELD [PAGE 696], AND THEIR ASSOCIATES)

DR. WILLIAM E. BLOOMER, New Haven, Conn.—It is a pleasure to discuss this very nice presentation by Dr. Littlefield. Working with Drs. Lindskog and Liebow, we became interested in the potential of the bronchial arterial supply after ligation of the unilateral pulmonary artery back in 1947.

This slide, I think, shows the extent to which bronchial arteries can increase in size on one side. You can see on this side, where there is no red injection, there is a lack of pulmonary arteries, and these black vessels represent the increased bronchial arterial supply on that side. This made us wonder if the potential of bronchial arteries might be applied to the coronaries in the old cardiopneumonopexy that was suggested and done by Lezius.

[Slide] In using this technique, we felt that this might supply arterialized blood to the lung and, by way of newly formed vessels across the transpleural plane, to the myocardium.

In this slide, one can see, in such an injection-corrosion specimen, newly formed vessels going from the coronary arteries into the pulmonary vessels, where the coronaries have been injected in red.

[Slide] This is also seen in this specimen, and here you see the pulmonary arteries have also been filled by way of the bronchial arteries when the aorta was injected in black, and the red and the black mix together here in the lingula where this has been applied to the heart.

I would like also to point out that not only is there a potential supply of blood by way of the bronchial arteries into an ischemic myocardium, but also this lung may form a bridging effect from one ischemic area of the heart to another, and we think this may be important.

[Slide] Not only were these transpleural vessels shown but, also, this very important, we think, retrocardiac plexus, which has been emphasized by Dr. Littlefield this morning. These vessels, injected in red here, represent connections between the bronchial arteries and the anterior and posterior left atrial arteries that arise from the left circumflex.

[Slide] Diagrammatically, then, it seems that the bronchial arteries, after ligation of the pulmonary artery, and having already preformed small connections between the coronary artery here, become greatly enlarged, and the same mouths that feed the bronchial arteries feed these retrocardiac vessels, which also feed the coronary arteries, and it seems that they do form a very important collateral flow.

I would like to emphasize that, as shown by Stern and Liebow's findings, one doesn't have to tie off the whole pulmonary artery; the lingular artery works fine. I understand that, although we have only begun to evaluate this in patients, Dr. Burford has started to incorporate this principle in some of his poudrage procedures, and we will be very interested in seeing his results.

DR. CHARLES P. BAILEY, Philadelphia, Pa.—I was particularly interested in Dr. Richard Hardy's presentation of a new elastomer foam prosthetic for arterial replacement. We didn't have any of that material, but we did have similar problems. One of the problems that he did not particularly mention was the difficulty of containing blood within such a prosthetic graft when the patient was heparinized. We have had this problem not only in replacement of peripheral arteries but in replacement of parts of the aorta, as when we use part of the aortic wall to repair the aortic valve.

[Slide] Dr. Edward Fitch, of our resident staff, devised this particular prosthetic material. It consists of two slabs of compressed Ivalon sponge with an intervening sheet of Teflon mesh, both of which are readily available. The three layers of the "sandwich" are compressed and autoclaved. They end up as a single thickness sheet with good adhesion of its various components. One then has the strength of the Teflon and its durability, and at the same time the advantages of handling of Ivalon sponge.

This is the material before compression, and you can see the tremendous difference in the thickness of the slabs of Ivalon before and after compression. This is compressed 15 to 1. The usual compression of Ivalon for septal defect repair is about 6 to 1.

At this compression there is no leakage of blood through the prosthetic material nor through the stitch holes that are created in sewing it to the arterial wall.

[Slide] This prosthetic can be made in tubular form, the inner slab being rather thin, as it is wrapped around the inner mold. The Teflon is wrapped around and then a thicker slab of Ivalon is added. Of course when it comes out of the mold it has a flange on either side and you ought to really cut off the flange for esthetic purposes as well as for ease of handling.

[Slide] This material can be made in the form of a bifurcation graft just as well, if you wish.

Using this material, either to replace segments of aortic wall that have been removed or in the replacement of an entire artery, we have found no unexpected difficulty. It is tolerated well by the tissues. We were afraid at first that the fibrous tissues of healing might not grow into the material and cause it to be thoroughly incorporated, but this fear has proved to be unfounded. At least connective tissue fibrils must penetrate into the porosity of the prosthesis, because it attaches well to all contiguous structures. Neither in the experimental animals in which this was worked out nor in human beings has there been any difficulty. If you don't have any of this new elastomer foam material you can easily make up a homemade prosthesis which will work quite well.

DR. PAUL W. SANGER, Charlotte, N. C.—The monumental work that Dr. Holman reported to this Society when he was President about 5 years ago on post-stenotic dilatation, I think, shall ever remain a pattern for studying this complex phenomenon.

It is quite true that there is definitely a turbulence in the post-stenotic dilatation area, but we have a different opinion as to the effect of this turbulence. We believe another hydrodynamic phenomenon called cavitation plays the most important role in the development of post-stenotic widening. Cavitation was originally described as "the boiling of water in a tube at ordinary temperature." Liquids flowing through a closed system generally contain gases in equilibrium with the fluid. When the pressure equilibrium becomes disturbed, there is a tendency for a cavity (bubble) formation. Under certain conditions, the sudden changes and alterations in velocity and pressure cause an alternate formation and collapse of gas bubbles. The human blood is a supersaturated fluid of oxygen, CO_2, and nitrogen. When there is a disturbance, innumerable small "micro-explosions" are created. The consequence of this long-acting process is severe injury to the walls of the system in which the fluid is flowing.

A long-continued bombardment of these "micro-explosions," we think [slide] results in destruction of the media of the artery. Note the fractionation of the elastic tissue. The bottom portion of this slide was taken from the same aorta just a few centimeters beneath the post-stenotic dilatation. You will see the normal histologic appearance of the artery.

The second slide demonstrates cavitation produced in a glass model. You will observe that just beyond the constricted portion of the tube are numerous gas bubbles. We believe the implosion or explosion of these gas bubbles causes severe injury to the vessel walls.

DR. PAUL NEMIR, JR., Philadelphia, Pa.—I rise to congratulate Dr. Hardy on his very nice presentation. Certainly this gives promise of at least getting us closer to the ideal prosthetic, because it would seem to obviate that factor which, at least in our hands, has been troublesome at times, that is, bleeding at the time of insertion of the prosthetic.

We have used a number of different substances, such as homografts, heterografts, nylon, Dacron, Teflon, and Ivalon in about 60 animals, implanting the material into the thoracic and abdominal aorta. As far as intimal replacement and fibroblastic proliferation are concerned, there is very little difference with respect to the materials which we have used when we have examined these animals after periods of as long as 12 to 13 months.

It would seem that the major problem would be to obviate the factor of bleeding at the time of insertion and this certainly gives promise of doing that.

DR. ROLLINS HANLON, St. Louis, Mo.—I would like to comment on the presentation of Dr. Read.

Some time ago we were interested in this problem of toxic factors in angiocardiography. We studied it in some 40 dogs, injecting 70 per cent Urokon in three areas of the circulatory system—the jugular vein, the right ventricle, and the pulmonary artery.

We found that the closer to the pulmonary parenchyma one injected the material, the greater was the incidence of deleterious reaction in the lung. We noted severe agglutinative thromboses in the dog's lung (similar to those described by Dr. Read) in about 85 per cent of the instances in which we injected Urokon into the pulmonary artery directly. We then suggested that caution should be exercised in selective angiocardiography in man when injections are made close to the pulmonary substance.

We therefore approached selective angiocardiography in patients with some caution. However, during the past 2 years I am happy to say that in something over 700 injections through an intracardiac catheter with 85 or 90 per cent Hypaque we have had no fatal or serious reactions. These injections were done by Dr. J. Gerard Mudd in his cardiac catheterization laboratory and the negligible reaction rate is probably associated with the fact that most injections were made with the catheter tip in the outflow tract of the right ventricle or in the left atrium, and only infrequently and with carefully reduced dosage into the pulmonary artery directly. Also, the contrast substance was not Urokon, as in our experimental studies.

DR. THOMAS C. MOORE, Indianapolis, Ind.—I, too, should like to comment upon the very interesting paper of Dr. Read.

We have been interested in studying the deleterious effects of intravascular radiopaque media in the laboratory at the Indiana University Medical Center and have carried out studies employing injection into the peripheral arteries of dogs. The response has been evaluated by means of the impedance plethysmograph. We found that dilute doses of radiopaque media tended to have a vasodilating effect, whereas concentrated doses had a very markedly constricting effect. However, with repeated large injections the vasoconstricting effect became progressively less in degree. We found, also, that repeated small injections tended to protect against the constricting effect of a subsequent larger injection.

In addition to these findings, we also discovered that a prior injection of procaine protected against this effect. This finding confirmed the observations of Dr. Keith Grimson with respect to injections into the renal arterial tree. It appears that the response to intravascular injection of radiopaque media may well be a constrictive one and probably not mediated through the sympathetic system.

Dr. Robert Shaw, of Boston, has shown clinically that this response occurs even in sympathectomized extremities. I think that the observations of Dr. Read may be quite helpful, indeed, in eliciting the actual mechanism of this response.

I should like to ask him if he has attempted to use repeated injections in his preparations, and whether he has attempted to use prior injections of procaine. It may well be that the response occurs as a result of some damaging effect of this medium on the red cells and that this vasoconstricting response may be actually secondary to red cell damage.

It also might be worth while to expose some blood to the media, to filter the red cells off and to see what the resulting plasma is able to do in the way of vasoconstriction. I think it is an exceedingly important and worth-while study.

Announcements

THE AMERICAN ASSOCIATION FOR THORACIC SURGERY

Notice of Annual Meeting

The Fortieth Annual Meeting of The American Association for Thoracic Surgery will be held May 11, 12, and 13, 1960, in Miami Beach, Florida. Headquarters will be the Deauville Hotel.

Requests for Hotel Reservations

These should be mailed directly to Mrs. Mildred Sander, Reservation Manager, Deauville Hotel, Miami Beach, Florida. Please mention this Association, the type of accommodation desired, the date, and approximate hour of arrival and departure. If accommodations are desired elsewhere please communicate directly with the hotel of your choice.

Material for the Program

SCIENTIFIC PAPERS.—Abstracts of all papers proposed for presentation at the 1960 meeting *must be received on or before* **November 15, 1959,** otherwise they will not be considered by the Program Committee. These should be labeled "For Thoracic Surgery Forum" or "For Regular Program" depending upon the nature of the subject matter, in the same manner as in previous years. They should contain from 200 to 250 words that accurately reflect the content of the completed paper.

Six, repeat, six clearly legible copies of *each* abstract must be sent to Miss Ada Hanvey, Administrative Assistant, The American Association for Thoracic Surgery, 308 Carondelet Building, 7730 Carondelet Avenue, St. Louis 5, Missouri.

Essayists selected for the program are reminded that papers presented at the meeting *must* be handed to the secretary *immediately* after their presentation. If they are not ready at that time there is a chance that they will not be published in THE JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY.

Applications for Membership

Applications for Associate Membership in the Association must be received by the Membership Committee *not later than* **November 15, 1959,** otherwise the application will be deferred for consideration until the 1961 meeting.

Applicants must be sponsored by three Active or Senior Members of the Association. In addition to the signature on the application form, the sponsors will forward a *separate* letter concerning the applicant directly to:

Frank Gerbode, M.D.
Chairman of the Membership Committee
Stanford University Hospital
San Francisco 15, California

Sponsors are reminded that *new* letters of recommendation must be forwarded to the Chairman of the Membership Committee should their applicants be held over for reconsideration a *second year.*